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HISTOPATHOLOGY OF DIARTHRODIAL JOINTS IN ANKYLOSING SPONDYLITIS

BY

B. CRUICKSHANK

From the Department of Pathology and the Rheumatic Research Unit, University of Edinburgh

The literature on the pathology of ankylosing spondylitis contains only three articles in which the histopathology of diarthrodial joints is described (Güntz, 1933; Freund, 1942; Collins, 1949). Furthermore, these papers are concerned mainly with pathologically late and clinically inactive stages of the disease and have few illustrations. Despite the lack of adequate pathological study, it is widely held that ankylosing spondylitis is a variant of rheumatoid arthritis, rather than a separate disease. The objects of this paper are therefore:

(*a*) to describe and illustrate in detail the histopathology of the diarthrodial joints in ankylosing spondylitis, particularly in clinically active cases,
(*b*) to discuss the relationship between ankylosing spondylitis and rheumatoid arthritis as they affect this type of joint.

Material

Tissue was obtained from twelve cases of ankylosing spondylitis. Three examples were from *post-mortem* studies, and the other nine were obtained at operation.

The first *post-mortem* case was exceptional in being clinically active at the time of death and in the number of joints involved. Practically every joint in the body was affected, most of them showing some degree of ankylosis. This case was extensively studied and histological examination included several blocks from the right knee, one from all joints of the first right toe and the right medial cuneiform-first metatarsal joint, several from each sacro-iliac joint, one from each sterno-clavicular joint, one from each of several costo-sternal joints, and several from the manubrio-sternal joint. The spinal column from the ninth thoracic to the third sacral vertebrae was removed at autopsy and blocks were taken from many intervertebral joints, intervertebral disks and the left tenth costo-vertebral joint. Many of the illustrations are taken from this case (Figs 8, 10-14, 16, 18).

Only axial joints were involved in the second *post-mortem* case; the spinal column from T3 to L4, the sternal joints, and the symphysis pubis were examined in detail.

The third *post-mortem* case was that already reported by Freund (1942), many sections from the lumbar vertebrae being available.

The operation material was obtained from the hips of six patients, and from the sterno-clavicular, sacro-iliac, and knee joints in one case each. The material from the hips, which consisted of the head of the femur, soft tissue, and acetabular tissue, was taken from both hips in three cases and from one hip only in the other three.

This material was compared with tissue from joints, bursae, and tendon sheaths from 42 cases of rheumatoid arthritis, 42 of other rheumatic diseases (including rheumatic fever, osteo-arthritis, gout, systemic lupus erythematosus, and polyarteritis

nodosa), 139 of non-rheumatic arthritis (including bacterial arthritis and synovial lesions associated with trauma and damage to menisci), 121 of bursitis, and 137 of tenosynovitis.

Results

Synovial Tissue.—The changes in the synovial tissue were seen at an early stage in some of the biopsies. It showed proliferation with an excessive number of villi plus hyperplasia of the surface cells, so that this layer was up to six cells deep in places (Figs 1 and 3). The cells were often increased in size, with considerable variation in the size, shape, and chromatin content of the nuclei. Multinucleate cells, sometimes much larger than the mononucleate cells, were present in two cases (Fig. 3), but no mitotic figures were seen. Occasional segments

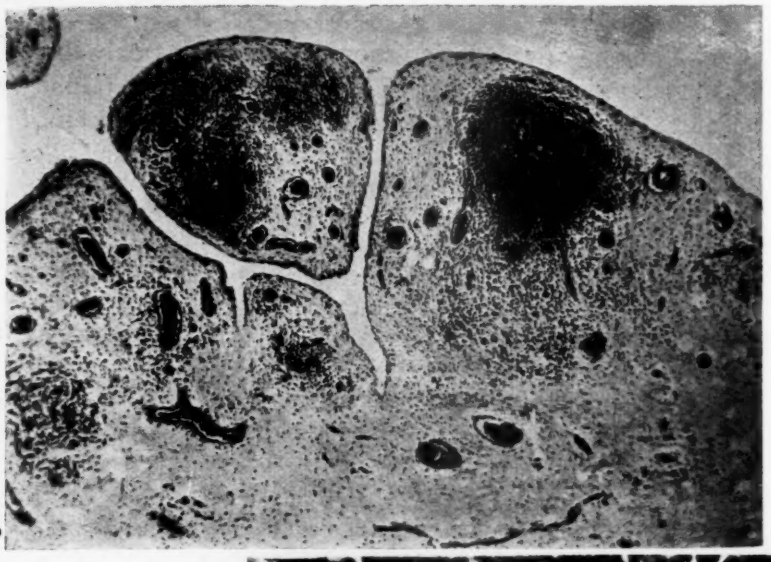

FIG. 1.—Synovial tissue from left hip. Villi increased in number and size, with slight proliferation and patchy necrosis of surface cells (left). Several large foci of lymphocytes and plasma cells are seen. Vessels markedly congested. Some oedema. (× 35.)

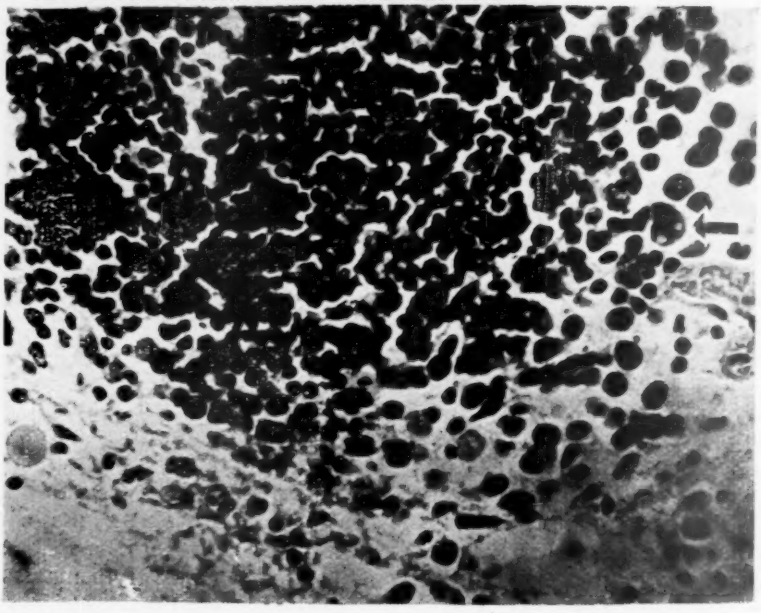

FIG. 2.—Same section as Fig. 1. High-power view of focus of lymphocytes and plasma cells. Arrow indicates Russell bodies associated with one plasma cell. (× 450.)

of the surface layer were necrotic (Fig. 1). Accompanying the hyperplasia, there were chronic inflammatory features, with marked congestion, oedema, and infiltration with lymphocytes, plasma cells, and histiocytes in that order of frequency. The cells were both diffuse and focal in distribution, with a distinct tendency to perivascular arrangement, particularly in the deeper parts of the synovial tissue and in the capsule (Figs 1, 2, and 3). Recent haemorrhage masked or distorted some of these features in several of the biopsies from the hips. Most of this, and probably much of the congestion in these specimens, was due to operative trauma, but the presence of haemosiderin in practically all the sections of synovial

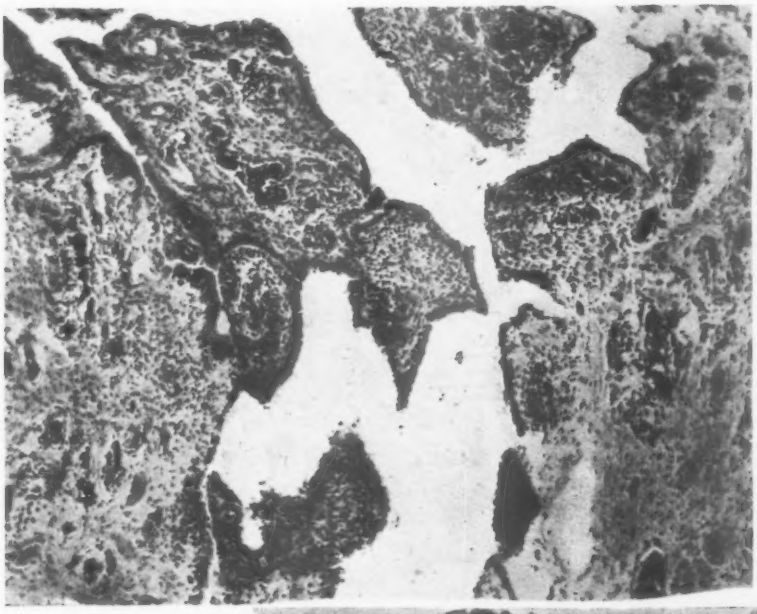

FIG. 3.—Synovial tissue from right hip. Proliferation of surface layer more striking and some giant cells visible at centre. (× 50.)

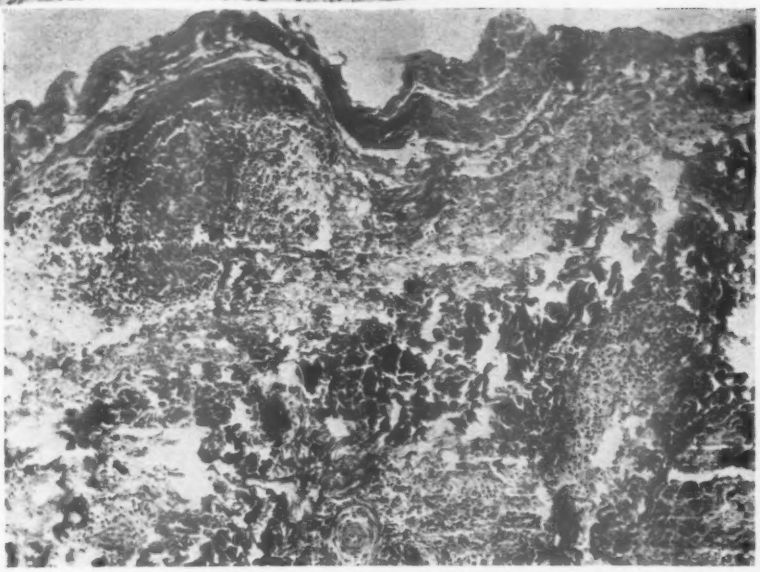

FIG. 4.—Synovial tissue from left knee. Marked fibrosis under surface (top), which has lost its lining layer. Fibrosis also present deeper. Focal round-cell infiltration still present. (× 50.)

FIG. 5.—Synovial tissue from R. or L. hip. Fibrous tissue showing metaplasia to cartilage. (× 50.)

FIG. 6.—Head of right femur. Articular surface mostly covered with thick layer of fibrous tissue. Tags of villous synovial tissue adhere to the neck.

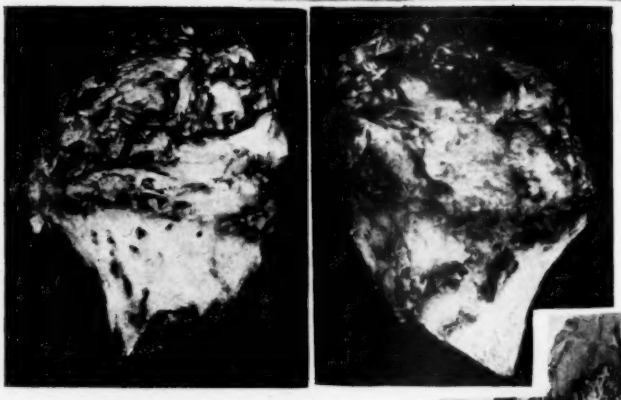

FIG. 7.—Head of left femur from same case as Fig. 6. No normal articular cartilage. Much of medial surface (left) completely denuded, proximal and lateral surfaces covered with thick layer of fibrous tissue. Arrow indicates eburnation at one point. (× 1½.)

tissue examined indicated that haemorrhage was a feature of the disease. Arterioles and small arteries frequently showed marked endarteritis obliterans and perivascular fibrosis. Several of the patients had received radiotherapy, so that some of these vascular changes were probably due to irradiation, rather than to the disease itself. At a later stage, fibrosis of the synovial tissue was a marked feature, but infiltration with

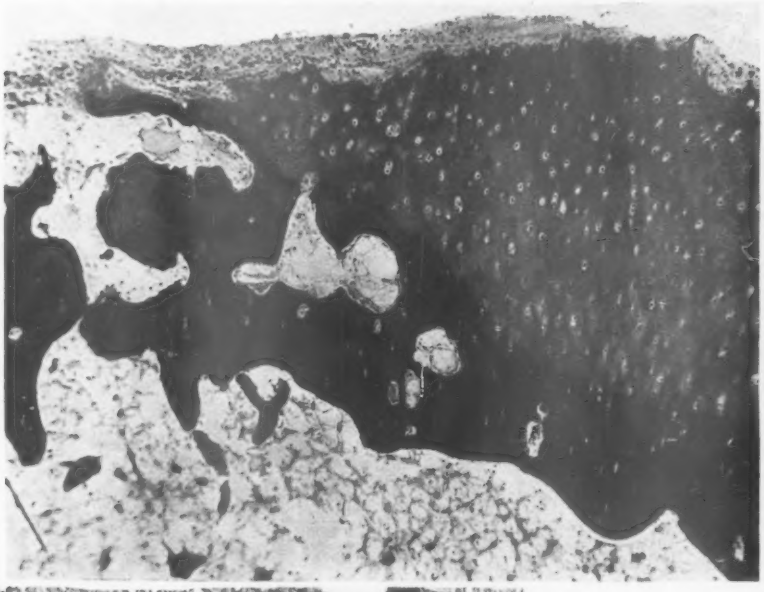

FIG. 8.—First *post-mortem* case. Medial condyle of right femur. Articular cartilage being destroyed by granulation tissue on its free surface. Some bony replacement of deepest part of cartilage. (× 30.)

FIG. 9.—Medial end of right clavicle. Bone end (left) has lost its covering of cartilage and is covered with a thick layer of vascular fibrous tissue, which has developed a synovial surface (right). A fragment of synovial tissue (top right) shows the same features. (× 50.)

chronic inflammatory cells was still seen (Fig. 4, p. 395), and vascularity was greater than normal (Fig. 9). Later still, when signs of inflammation were disappearing, the fibrous tissue showed foci of metaplasia to cartilage and bone (Fig. 5).

Articular Cartilage and Bone.—The articular cartilage became covered with a layer of granulation tissue continuous with the proliferating synovial tissue, and of variable thickness and constitution. Inflammatory changes predominated in the earlier stages (Figs 8 and 10), to be replaced gradually by fibrous tissue (Figs 6, 7, and 9), in which foci of metaplasia occurred as already described. In

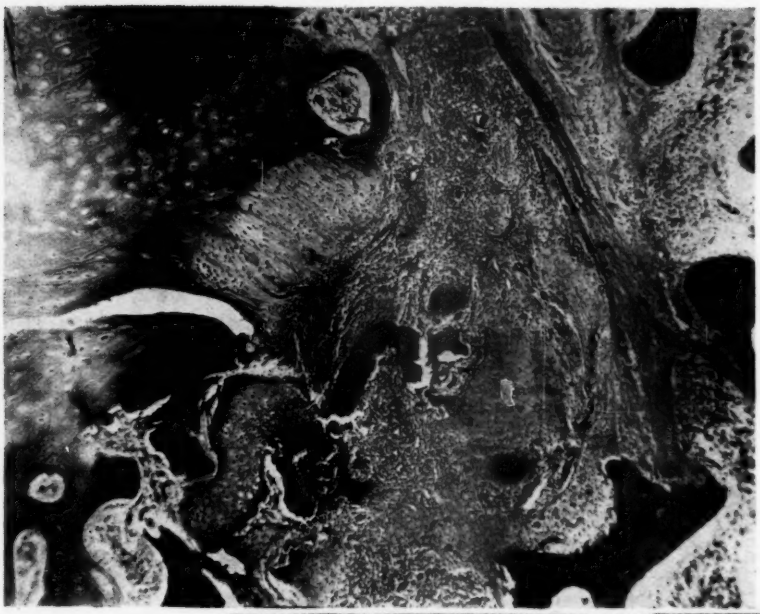

FIG. 10.—First *post-mortem* case. Right fourth costosternal joint. Vascular fibrous tissue uniting costal cartilage (top left) to sternum, contains focal and diffuse round cells, with patches of metaplasia to cartilage and bone (centre left). (× 30.)

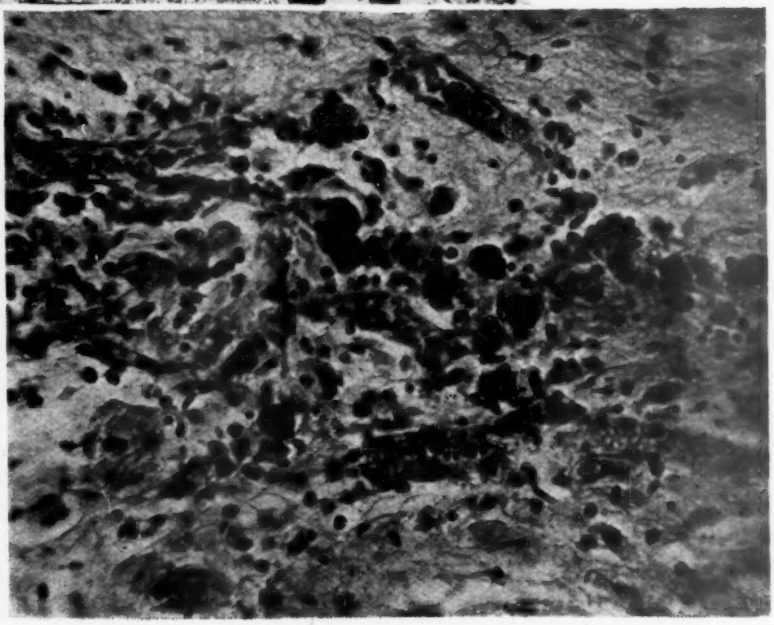

FIG. 11.—First *post-mortem* case. Left third costosternal joint. Many lymphocytes and plasma cells have fragmented nuclei. (Large, dark areas show presence of haemosiderin.) (× 250.)

two cases, a simple synovial surface had developed on the free surface of this granulation tissue (Fig. 9). The underlying cartilage was gradually destroyed and, when bone was reached, this suffered the same fate. Penetration of the subchondral plate and invasion of the adjacent cancellous spaces were sometimes seen without extensive destruction of the bone (Figs 9 and 10). Focal infiltration with lymphocytes and plasma cells was common in cancellous spaces in bones near affected joints, even in the absence of penetration of granulation tissue into the

FIG. 12.—First *post-mortem* case. Right medial cuneiform—first metatarsal joint. Almost complete destruction of cartilage and ankylosis by fibrous tissue. (× 25.)

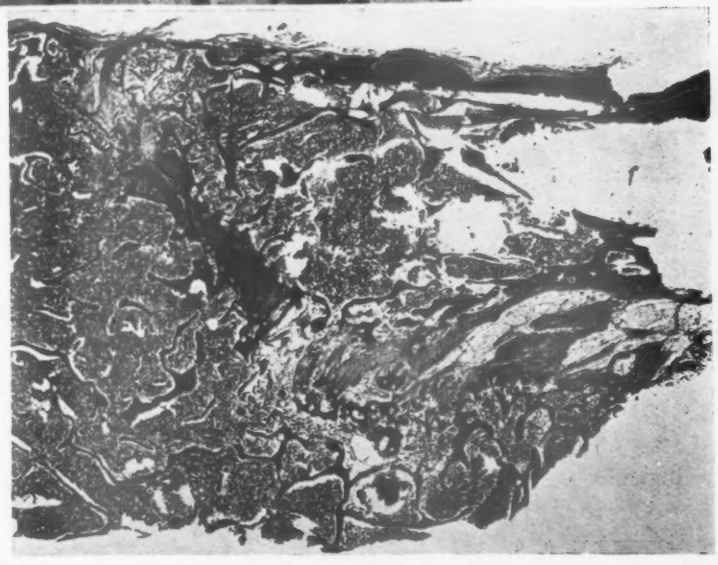

FIG. 13.—First *post-mortem* case. Left tenth costo-vertebral joint. In the upper part of the figure, the joint has been replaced by fibrous tissue. Below this a partial joint space may be seen. (× 4.)

bone. Endarteritis obliterans was particularly marked in this situation in the sternoclavicular joint of one case, but this joint had been irradiated. The presence of large numbers of fragmented plasma cells in this case was probably also an irradiation effect (Fig. 11). Considerable atrophy of the cancellous bone in the neighbourhood of affected joints was a constant feature (Figs 7 and 12). In the single biopsy from the sacro-iliac joint, a little granulation tissue was present over the surface of the hyaline cartilage, but no synovial tissue proper was seen. A good deal of well-formed fibrous tissue between two surfaces covered by hyaline cartilage probably represented normal intra-articular ligaments. It was difficult to be certain of this, for the specimen was small and not easy to orientate.

FIG. 14.—First *post-mortem* case. Joint between third and fourth lumbar vertebrae on left side. Joint space contains haemopoietic marrow, and remnants of articular cartilage are undergoing direct metaplasia to bone. (× 30.)

The late stages were characterized by ankylosis, which was usually of mixed fibrous and bony, or purely bony, type (Figs 12, 13, 15, 16, 17, 18). Evidence of metaplasia to bone was seen even in those joints in which the bones were joined mainly by fibrous tissue (Fig. 12). In the final stage, practically none of the original joint tissues persisted, their place being taken by cancellous bone with haemopoietic marrow. Scattered islands of cartilage, undergoing gradual replacement by bone, were the only indication of the position of the joint (Figs 14 and 18). In those cases where ankylosis was partial or absent, changes of osteoarthritis were superimposed, namely, eburnation of exposed bone with marginal osteophytes (Fig. 7).

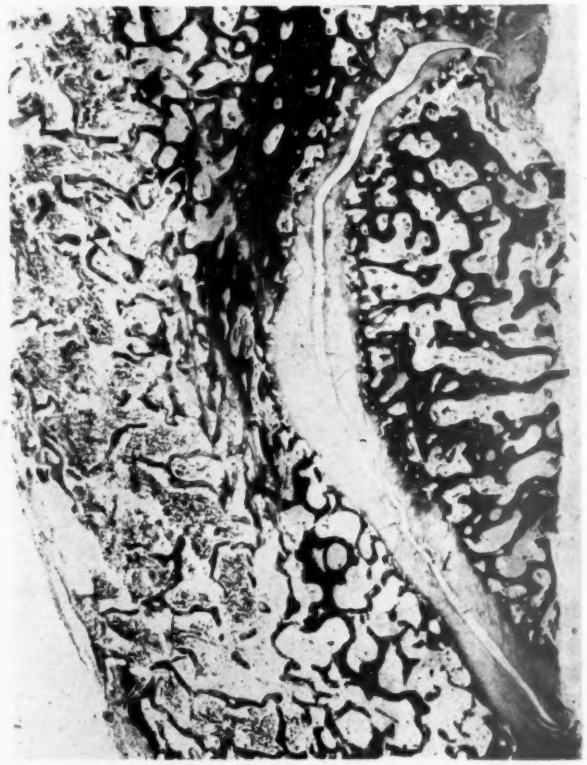

FIG. 15.—Normal lumbar intervertebral joint. (× 7.)

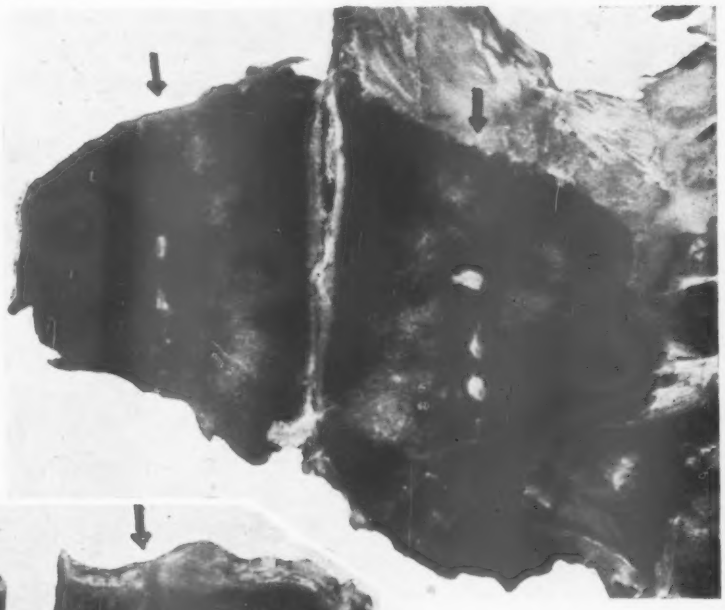

FIG. 16.—First *post-mortem* case. Right sacro-iliac joint, sawn open by a coronal cut. Only a few islands of cartilage remain. Arrows indicate joint line.

FIG. 17.—Normal sacro-iliac joint, opened in the same way as specimen in Fig. 16.

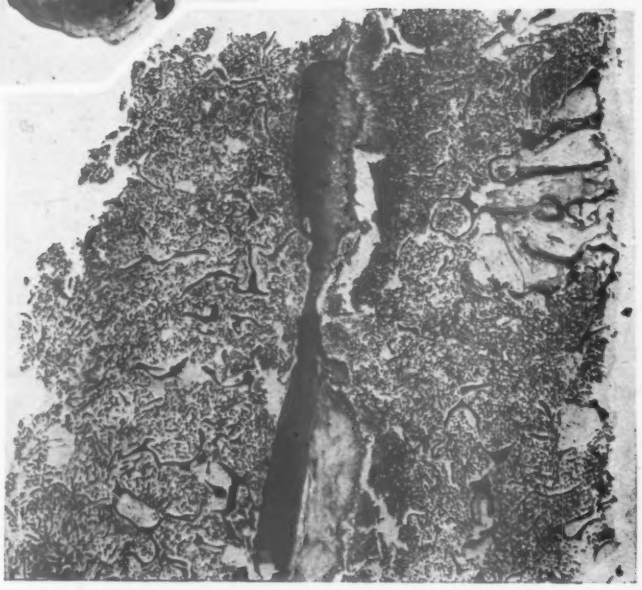

FIG. 18.—First *post-mortem* case. Left sacro-iliac joint. Vertical section showing single remaining cartilaginous plate. (× 7.)

Other Joint Structures.—The joint capsule showed changes in parallel with those in the synovial tissue, though the inflammatory changes were less marked. Intra-articular ligaments and menisci were destroyed along with the articular cartilages.

Discussion

It has been possible to trace the sequence of events in the diarthrodial joints in ankylosing spondylitis. Although none of the cases examined was early in the chronological sense, this is a disease of slow progression, characterized by phases of increased activity, so that material representing active phases may be obtained long after the first onset of the disease.

The disease apparently begins in the synovial tissue as a subacute or chronic inflammation, associated with proliferation, producing an excessive number of villi with a thickened lining of synovial cells. Proliferation also occurs over the surface of the articular cartilage and other intra-articular structures. Granulation tissue* is formed which destroys the cartilage and later penetrates the underlying bone. Opposing layers of this granulation tissue frequently become adherent and, as the inflammation subsides, firm fibrous ankylosis is established. In this disease, the ankylosis usually becomes bony. These features are closely similar to those seen in rheumatoid arthritis and are the basis for the current opinion that ankylosing spondylitis is a variant of rheumatoid arthritis (Dunham and Kautz, 1941; Polley and Slocumb, 1946; Collins, 1949).

There can be no doubt that the lesions in the diarthrodial joints in the two diseases are very alike. It has been possible to match all the stages of ankylosing spondylitis with sections from cases of rheumatoid arthritis. Although the process was more intense in several of the cases of rheumatoid arthritis, the differences are of degree only and probably reflect greater activity of the disease in these cases. Certain minor differences, however, were seen between the two conditions. Firstly, there was a greater tendency to haemorrhage in ankylosing spondylitis, perhaps due to the earlier formation of adhesions which were broken down on subsequent movement. Secondly, thickening of small vessels, usually in the form of endarteritis obliterans, was more marked in ankylosing spondylitis, even in joints which had not been irradiated. In those which had been irradiated, it was often a prominent feature. Thirdly, spondylitis is characterized clinically by a marked tendency to ankylosis soon after the involvement of a joint, and this process often goes on to bony fusion of the joint, as seen in radiographs. This was reflected in the pathological material examined. On the other hand, bony ankylosis is quite uncommon in rheumatoid arthritis.

The close resemblance between the joint lesions in the two diseases is open to two alternative interpretations:

(*a*) that ankylosing spondylitis and rheumatoid arthritis are variants of one disease,

* It is unfortunate that the term " pannus " is generally reserved for the tissue found on the surface of the articular cartilage in rheumatoid arthritis only, for the same process is seen in various other chronic arthritides, such as tuberculosis and chronic septic arthritis. " Pannus " is merely granulation tissue flattened out by its anatomical position.

(*b*) that they are separate diseases, the pathological lesions representing a common reaction to different aetiological factors.

The former argument is based mainly on this resemblance in the pathology. The two conditions differ in respect of sex incidence, anatomical distribution of the lesions in typical cases, and response to therapeutic measures. In a few cases, such as the first *post-mortem* case in this study, ankylosing spondylitis involves peripheral limb joints as well as axial and limb girdle joints. It such cases are seen only in the late stages, the clinical resemblance to rheumatoid arthritis is striking. In the most cases of this type, however, the early stages of the disease are clinically typical of spondylitis. Pathologically also, there are differences, for the characteristic subcutaneous nodules of rheumatoid arthritis have not been encountered in ankylosing spondylitis. The muscle and nerve lesions which were seen in a high proportion of cases of the former type (Cruickshank, 1952), were seen only rarely in cases of the latter type.

On the other hand, there are numerous examples of conditions due to differing aetiological factors in which the lesions resemble one another closely. Furthermore, changes in the synovial tissue identical with, or closely resembling, those of ankylosing spondylitis and rheumatoid arthritis were seen in patients in whom both diseases could be excluded. Such changes were seen in one case of systemic lupus erythematosus, in eleven of non-rheumatic arthritis, in one of bursitis, and in seven of non-specific tenosynovitis. Another 21 of the 78 cases of non-specific tenosynovitis showed some or all of the features seen in the synovial tissue in ankylosing spondylitis and rheumatoid arthritis. In these cases the clinical notes were not available, but in all of them the tenosynovitis appears to have been an isolated process. Tenosynovitis is quite unusual in rheumatoid arthritis or ankylosing spondylitis, having been noted only once in several hundred cases seen in the last three years at the Rheumatic Unit, Northern General Hospital, Edinburgh.

The similarity between the histopathology of the diarthrodial joints in ankylosing spondylitis and rheumatoid arthritis can, therefore, be explained as a common response to different, but perhaps related, aetiological factors. Until more is known about these factors, it does not seem justifiable to classify ankylosing spondylitis as a variant of rheumatoid arthritis.

Summary

(1) Tissue was examined from diarthrodial joints from twelve cases of ankylosing spondylitis, 42 cases of rheumatoid arthritis, and 42 cases of other rheumatic diseases, and also from joints, tendon sheaths, and bursae from 397 cases of non-rheumatic diseases.

(2) The lesions found in ankylosing spondylitis were: subacute or chronic inflammation and hyperplasia of the synovial tissue; destruction of articular cartilage and other intra-articular tissues by granulation tissue. In the later stages, ankylosis, usually of bony type, occurred.

(3) The pathological changes in the diarthrodial joints in ankylosing spondylitis resemble very closely those of rheumatoid arthritis, but the two diseases differ

in other important respects. Changes identical with those of ankylosing spondylitis and rheumatoid arthritis, or closely resembling them, were seen in joints, bursae, and tendon sheaths in cases where both diseases could be excluded.

(4) The classification of ankylosing spondylitis as a variant of rheumatoid arthritis is not justifiable until more is known about the aetiology of the two diseases.

This work was carried out during the tenure of a research grant from the Nuffield Foundation. I wish to thank Professor A. M. Drennan for providing facilities, and Dr. R. F. Ogilvie for advice and criticism. The sections were prepared by Mr. E. Kaminski and the photographs taken by Mr. T. C. Dodds.

References

Collins, D. H. (1949). "The Pathology of Articular and Spinal Diseases", pp. 313-327. Arnold, London.
Cruickshank, B. (1952). *J. Path. Bact.* **64**, —. (In the press.)
Dunham, C. L., and Kautz, F. G. (1941). *Amer. J. med. Sci.*, **201**, 232.
Freund, E. (1942). *Edin. med. J.*, **49**, 91.
Güntz, E. (1933). *Fortschr. Röntgenstr.*, **47**, 683.
Polley, H. F., and Slocumb, C. H. (1947). *Annals of the Rheumatic Diseases*, **6**, 95.

L'histopathologie des diarthroses dans la spondylite ankylosante

Résumé

(1) On a examiné les tissus des diarthroses dans 12 cas de spondylite ankylosante, 42 cas d'arthrite rhumatismale, et 42 d'autres maladies rhumatismales, ainsi que les tissu provenant d'articulations, de gaines tendineuses et de membranes synoviales de 397 cas de maladies rhumatismales.

(2) On a trouvé dans la spondylite ankylosante les lésions suivantes: inflammation subaiguë ou chronique et hyperplasie du tissu synovial, destruction par le tissu de granulation du cartilage articulaire et des autres tissus intra-articulaires. A une période ultérieure il se produisait une ankylose, généralement du type osseux.

(3) Les altérations pathologiques dans les diarthroses des cas de spondylite ankylosante ressemblaient de très près à celles des cas d'arthrite rhumatismale, mais ces deux maladies différaient entre elles par d'autres aspects importants. Des altérations identiques ou bien fort similaires à celles de la spondylite ankylosante et de l'arthrite rhumatismale ont été observées dans les articulations, les synoviales et les gaines tendineuses des cas où les deux maladies ont pu être exclues.

(4) La classification de la spondylite ankylosante comme une variante de l'arthrite rhumatismale n'est pas justifiable jusqu'à ce qu'on connaisse mieux l'étiologie de ces deux maladies.

La histopatología de las diartrosis en la espondilitis anquilosante

Sumario

(1) Se ha examinado los tejidos de las diartrosis en 12 casos de espondilitis anquilosante, en 42 casos de artritis reumatoide, y en 42 casos de otras enfermedades reumáticas, as como los tejidos procedentes de articulaciones, de vainas tendinosas y de membranas sinoviales de 397 casos de enfermedades otras que reumáticas.

(2) Las lesiones siguientes fueron encontradas en la espondilitis anquilosante: inflamación subaguda o crónica e hiperplasia del tejido sinovial, destrucción por el tejido de granulación del cartilago articular y de otros tejidos intra-articulares. En los periódos avanzados hubo anquilosis, generalmente de tipo óseo.

(3) Las alteraciones patológicas en las diartrosis de los casos de espondilitis anquilosante se parecían mucho a las observadas en los casos de artritis reumatoide, pero estas dos enfermedades diferían entre sí por otros aspectos importantes. Alteraciones idénticas o muy similares a las de la espondilitis anquilosante y de la artritis reumatoide fueron observadas en articulaciones, sinovias y vainas tendinosas de los casos en que la existencia de ambas enfermedades había podido excluirse.

(4) La clasificación de la espondilitis anquilosante entre las variantes de la artritis reumatoide no es justificable mientras no se conozca la etiología de ambas enfermedades.

THE CHANGING PATTERN OF RHEUMATOID ARTHRITIS

BY

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The introduction by Hench, Kendall, Slocumb, and Polley (1949) of 17-hydroxy-11-dehydrocorticosterone (" Compound E "; " Cortisone ") as a therapeutic measure in the management of rheumatoid arthritis, has aroused world-wide interest in the pathogenesis of this ancient disease.

Since 1859, when A. B. Garrod first proposed the name rheumatoid arthritis, our knowledge of the pathological processes underlying the disease has progressed slowly, but the introduction of cortisone has added a much-needed impetus to research in this field.

In the past, rheumatoid arthritis has been regarded as a non-suppurative polyarthritis of unknown aetiology (Davidson, 1948). Recently, a broader outlook has been adopted, and the question has been raised whether the condition is in itself a single entity, or is a name given to a group of closely linked clinical pictures. Kersley (1947) has observed that, whilst many cases of rheumatoid arthritis appear to be clearly defined, there are many intermediate cases, and many common factors. In this way, the concept of " rheumatoid variants " has arisen, and in presenting this paper, I hope to strengthen the concept that rheumatoid arthritis is not a single disease entity, but a tissue reaction pattern of multiform character. The basic tissue reaction is probably produced as a result of the interaction between the body defence mechanisms and various noxa. According to Selye (1948, 1949), the defence mechanism revolves around the pituitary-adrenal axis, and the noxa are defined as various forms of stress.

The present paper is confined to a description of two clinical pictures—Sjögren's disease and Reiter's syndrome. In a further communication to be published later, it will be suggested that there are at least six other syndromes which adhere closely to the basic tissue reaction pattern associated with rheumatoid arthritis. This last, which is fairly well defined, may be regarded as the parent or foremost example of this abnormal tissue reaction; the other less well defined clinical syndromes or variants merit further study, since analysis of them may further promote our still scanty knowledge of the parent condition.

Sjögren's Disease

In 1933, Henrik Sjögren, of Jönköping, Sweden, described from the ophthalmological point of view, a syndrome which now bears his name. Ellman

and Parkes Weber (1949) point out that the syndrome in its complete form includes xerostomia, rhinitis sicca, pharyngitis sicca, gastric anacidity, and polyarthritis of the rheumatoid type, as well as keratoconjunctivitis sicca, but patients rarely present with all these lesions.

The syndrome is a rare condition, and has a well-marked predilection for the female sex. It occurs maximally between the ages of 40 and 65 years. The patient complains of dry smarting eyes, dryness of the nasal, buccal, and pharyngeal mucosae with reduction of the salivary flow, and hoarseness (Stenstam, 1947). The salivary glands are palpably enlarged, and in about 80 per cent of cases the joints show changes characteristic of rheumatoid arthritis. Sorsby (1946) considers arthritis to be an integral feature of the syndrome, and hesitates to diagnose keratoconjunctivitis sicca in the absence of joint lesions. Parkes Weber (1945) has added to the syndrome: cough (from dryness of mouth and pharynx), achlorhydria, dryness of the skin, dryness and atrophic changes in the vagina, alopoecia, and Raynaud-like blueness of hands and feet; Sheldon (1939) reported "scleroderma-like" changes in the legs in association with Sjögren's disease. These features, together with a hypochromic anaemia, and an intermittent low-grade pyrexia, complete the picture presented by this condition.

Reiter's Syndrome

This syndrome was reported by Reiter (1916), who described the triad (polyarthritis, conjunctivitis, and urethritis) occurring quite apart from venereal infection.

The condition is said to occur predominantly in young males, and may run a protracted course characterized by long periods of remission (Harkness, 1947a). This triad may occur in association with dysenteric infections, and in drug and serum sensitization (Cohen, 1948). Harkness (1947a) differentiates the syndrome into two categories—venereal and dysenteric. The aetiology remains unknown, although viruses, pleuropneumonia-like organisms (Harkness, 1947b), a spirillum, and the Flexner-bacillus (Wood, 1946) have all been incriminated. Lydon (1947) has differentiated the syndrome from abacterial pyuria.

The conjunctivitis is bilateral, and iritis may occur. Polyarthritis and a copious urethral discharge occur at some stage during the illness. No causal organisms have been isolated from the conjunctival or urethral discharges, and culture of the joint effusions is invariably sterile. Pyrexia, hypochromic anaemia, and acceleration of the erythrocyte sedimentation rate are also features of this condition.

Case Reports

Case 1, married woman, aged 58.—She was admitted to hospital in May, 1950, suffering from a severe corneal ulcer affecting the left eye, and rheumatoid arthritis. She recollected no family history of arthritis or psoriasis, but one of her daughters had suffered from infantile eczema, and later, from asthma.

Her life had been uneventful and there were no relevant past illnesses. The menopause occurred at age 47, and 18 months later arthritis commenced in her right shoulder. The disease spread rapidly to her hands, wrists, and elbows, and within the year her feet, ankles, and knees, became involved. During this time she lost 1½ st. (9·4 kg.) in weight.

In spite of her disability she had remained ambulant, the arthritis having waxed and waned in severity down the years.

Four years ago she had complained of a "dry and crumby" sensation affecting both eyes, accompanied by mild photophobia. Two years ago the vision in the right eye was much reduced, by scarring of the cornea by a large ulcer. One year ago she noticed a similar dryness of her nasal, buccal, and pharyngeal mucosae, together with bilateral enlargement of the parotid glands. When conversing with friends she had to take frequent sips of water to moisten her dry mouth and tongue, and apart from an occasional dry crust, she had noticed no nasal secretion during the past 12 months.

Examination.—She was of poor physique, with sweating, cold extremities. Her mucosae were pallid, but there was no koilonychia or clubbing of the fingers. Inspection of the mouth, tongue, and pharynx confirmed the dry sensation which she complained of. Her skin was dry, apart from the damp, atrophic condition of her extremities. The nasal mucosa appeared normal, but was dry and lacked lustre. A large, penetrating corneal ulcer could be seen on the left eye, the right cornea being scarred by a similar ulcer in the past. The parotid and submaxillary glands on either side were palpably and visibly enlarged.

Examination of the joints revealed changes characteristic of rheumatoid arthritis, affecting the proximal interphalangeal joints of the fingers, metacarpophalangeal joints, wrists, elbows, and shoulders. Ulnar deviation of the fingers was noted. Similar changes were found involving the knees and ankles. Subcutaneous nodules were present on the olecranon ridge, and in the pad of the left thumb. The pulse rate was regular at 82 beats per minute. The heart was not clinically enlarged, but there was a well-marked presystolic murmur, accompanied by a palpable thrill, at the mitral area. Brachial blood pressure was 130/70 mm. Hg. Auscultation of the lungs revealed the presence of numerous persistent, fine crepitations, chiefly basal in distribution, and more pronounced on the right side. The spleen was palpably enlarged, extending at least three fingers below the left sub-costal margin. The superficial lymph nodes were not palpably enlarged, and no other abnormality was detected.

Laboratory Investigation

Blood count, *May 1.*—Haemoglobin 58 per cent.;
Red blood cells 4,100,000 per c.mm.;
Colour index 0·7;
White blood cells 2,500 per c.mm. (polymorphs 51, eosinophils 4, lymphocytes 26, monocytes 19 per cent.).

Erythrocyte sedimentation rate 50 mm. in one hour (Westergren).

Urine analysis, glucose tolerance test, and blood uric acid all normal.

Fractional test meal revealed the presence of a small quantity of free acid during the first hour of the test.

Achlorhydria developed after this time.

Radiological investigation revealed changes typical of rheumatoid arthritis in the carpus and fingers of both hands. The chest was screened, and no abnormality was detected in the lungs.

A barium swallow confirmed the presence of left auricular enlargement due to mitral stenosis.

Thymol turbidity, 6 units.

Weltmann coagulation reaction, 7.

Cephalin-cholesterol flocculation, ++++.

Two further blood counts were done in view of the leucopenia detected in the first count:

May 8.—Haemoglobin 70 per cent.;
Red blood cells 4,500,000 per c.mm.;
Colour index 0·8;
White blood cell 2,000 per c.mm. (polymorphs 50, lymphocytes 46, monocytes 4 per cent.).

June 6.—Haemoglobin 70 per cent.;
Red blood cells 4,540,000 per c.mm.;
Colour index 0·7;
White blood cells 1,000 per c.mm. (polymorphs 47, eosinophils 4, lymphocytes 41, monocytes 8 per cent.).

A second sedimentation rate done one month after the first revealed 43 mm. in one hour (Westergren).

Electrocardiogram—Bifid P waves Lead 2 and 3, plus a ventricular extra systole in Lead 3.

The patient was discharged from hospital after 8 weeks' treatment.

During this period an occasional elevation of body-temperature had been noted, and attributed to the presence of active arthritis. The Wassermann reaction was consistently negative.

Case 2, man, aged 35.—He was admitted to hospital in September, 1950, complaining of pain in the soles of his feet, ankles, spine, left shoulder, and left elbow. He was a farmer, and his past history was irrelevant apart from an injury to his left elbow when he was five years of age. The only illnesses which he could recall in the past were occasional attacks of "asthma" provoked by certain foodstuffs, and angioneurotic oedema. There was no family history of allergy, but one uncle (maternal) had rheumatoid arthritis. His present complaint commenced when he was 22 years of age. The illness was ushered in by an acute attack of bilateral iritis; his eyes were red, painful, and felt "gritty". After a few days he developed a copious urethral discharge, and this was followed by the onset of polyarthritis. The arthritis commenced in his feet and subsequently spread to involve all his joints, including the temporo-mandibular articulations. The larger joints were swollen with effusion and painful, and spindle-like swellings were noted on the fingers. He was transferred to hospital, where he remained for 2 months. When discharged, the iritis, urethritis, and arthritis had subsided, and this remission persisted for about 2 years. He subsequently relapsed and the triad of symptoms returned. The arthritis and urethritis subsided after 1 month, but the iritis persisted, with subsequent deterioration of vision.

In 1940, he was seen by a venereologist who excluded venereal disease as a cause for his complaint, and confirmed the diagnosis of Reiter's disease. During the war years he suffered minor relapses, and on one occasion was treated with massive doses of penicillin, without benefit. In October, 1949, an iridectomy was performed on the left eye by Dr. D. L. Charters, M.B.E.

During the present year, the iritis has been quiescent, and there has been no urethral discharge. For over 3 months he has complained of pain in his feet and ankles, and pain and stiffness in his shoulders and left elbow. There has been no loss of weight, but he has little desire for food.

Examination.—The typical asthenic habit, pallor, and peripheral circulatory inadequacy characteristic of the "rheumatoid diathesis" were noted. The extremities were cold and sweating, and the skin felt damp and atrophic. The stigmata of previous attacks of iritis were noted, but no active disease was present in the eyes. No discharge could be expressed from the urethra, and the genitalia were normal. The left ankle was swollen, and movement limited, similar findings being recorded in the shoulder joints and left elbow. No other abnormal signs were elicited in any system. Brachial blood pressure 110/70 mm. Hg. During his stay in hospital he ran a low-grade pyrexia, and for one week a burst of activity occurred in his knee joints, which became swollen with effusion, and painful. Streptomycin 4 g. daily for 5 days produced no benefit, but pregnenolone 100 mg. daily appeared to coincide with an improvement in his condition.

Laboratory Investigation

Blood count: Haemoglobin 60 per cent.;
Red blood cells 4,250,000 per c.mm.;
Colour index 0·7;
White blood cells 8,000 per c.mm. (polymorphs 70 per cent.).

Erythrocyte sedimentation rate 60 mm. in one hour (Westergren).

Urine analysis, agglutination reactions, fractional test meal, and flocculation tests all normal.

On one occasion a few pus cells were encountered in the urine.

Radiological investigation revealed a dislocation of the head of the left radius, probably the result of an old injury. The remainder of the skeleton showed decalcification of the bones.

A second sedimentation rate one month after the first revealed a drop of 59 mm. in one hour (Westergren).

Blood uric acid normal.

Weltmann coagulation reaction—5.

Wassermann and gonococcal complement-fixation reactions negative.

Transfusions subsequently raised the red cell count to:
Haemoglobin 80 per cent.;
Red blood cells 4,500,000;
Colour index 0·9.

Discussion

The first case represents a unique example of the rheumatoid reaction pattern. Analysis of the case reveals that the composite picture is made up of the following elements:

(*a*) Felty's syndrome: leucopenia, splenomegaly, polyarthritis.

(*b*) Sjögren's disease: polyarthritis, salivary gland enlargement, and characteristic " sicca " changes.

(*c*) Necrobiotic nodules of the rheumatoid arthritis type (Parkes Weber, 1947).

(*d*) Rheumatoid arthritis: the articular changes are characteristic of this condition.

(*e*) Mitral stenosis: although there is no previous history of chorea or acute rheumatism, the assumption is that this is rheumatic valvular heart disease. In view of the absence of a previous history of rheumatism, and the widespread nature of the lesions in this case, the possibility of the valvular lesion being of a rheumatoid nature cannot be excluded (Baggenstoss and Rosenberg, 1941).

In this patient then, the joints and periarticular tissues, skin and subcutaneous tissues, blood, reticulo-endothelial system, salivary glands, various mucosal surfaces, and possibly the mitral valvular endothelium constitute the tissue-reaction-pattern.

The second case introduces yet another tissue (the iris) into the general reaction-pattern of joints and periarticular tissues, blood, and mucosal surfaces. There can be little doubt in this case that rheumatoid arthritis and the so-called Reiter's syndrome, are indissolubly merged, one with the other, thus producing a composite picture. The iritis and urethritis have been quiescent for over one year, but the patient's sparse frame, elevated sedimentation rate, hypochromic anaemia,

polyarthritis, and occasional pyrexia, indicate the presence of active rheumatoid disease.

Conclusions

It would appear that the above cases confirm Kersley's suggestion that there exist many cases of rheumatoid arthritis which are ill-defined, and in which there appear to be many common factors. The segregation of these intermediate cases as entities of unknown aetiology is to be condemned. The use of such terms as Felty's syndrome, Sjögren's disease, and Reiter's syndrome has in the past hampered the progress of research, as these conditions have been mistakenly regarded as separate entities, all of unknown aetiology. The introduction of cortisone, together with the recognition that these syndromes merely represent deviations from the standard pattern of tissue reaction encountered in rheumatoid arthritis, should further promote our advancing knowledge of the underlying pathology of this disease.

Summary

The concept of rheumatoid arthritis as a tissue reaction pattern of multiform character is introduced. Brief descriptions are given of two varieties of this abnormal tissue reaction: Sjögren's disease and Reiter's syndrome.

Cases illustrating examples of each are described in the light of this theory. The first case represents a unique example of the many tissues and systems which may be involved in the rheumatoid reaction-pattern. The second case, which at present represents a typical case of rheumatoid arthritis, had undoubtedly begun as an equally typical case of Reiter's syndrome.

The use of such terms as Felty's syndrome, Sjögren's disease, and Reiter's syndrome is deprecated, since it leads to the segregation of these conditions as individual entities of unknown aetiology, whereas they are in fact only variants of the same pattern of tissue reaction.

I am indebted to Dr. D. L. Charters, M.B.E., for kindly allowing me access to his cases.

References

Baggenstoss, A. H., and Rosenberg, E. F. (1941). *Arch. intern. Med.*, **67**, 241.
Cohen, H. (1948). In "Textbook of the Rheumatic Diseases", ed. W. S. C. Copeman, ch. 13. Livingstone, Edinburgh.
Davidson, L. S. P. (1948). *Ibid.*, ch. 10.
Ellman, P., and Weber, F. Parkes (1949). *Brit. med. J.*, **1**, 304.
Garrod, A. B. (1859). "Nature and Treatment of Gout and Rheumatic Gout". Walton and Maberly, London.
Harkness, A. H. (1947a). *Brit. med. J.*, **1**, 72.
—— (1947b). *Ibid.*, **1**, 611.
Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F. (1949). *Proc. Mayo Clin.*, **24**, 181.
Kersley, G. D. (1947). *Brit. med. J.*, **1**, 347.
Lydon, F. L. (1947). *Ibid.*, **2**, 975.
Reiter, H. (1916). *Dtsch. med. Wschr.*, **42**, 1535.
Selye, H. (1948). *Ann. intern. Med.*, **29**, 403.
—— (1949). *Practitioner*, **163**, 393.
Sheldon, J. H. (1939). *Proc. roy. Soc. Med.*, **32**, 255.

Sjögren, H. (1933). *Acta. ophthal., Kbh.*, supp. 2, pp. 1-151.
Sorsby, A. (1946). *Brit. med. J.*, **1**, 774.
Stenstam, T. (1947). *Acta med. scand.*, **127**, 130.
Weber, F. Parkes (1945). *Brit. J. Ophthal.*, **29**, 299.
—— (1947). "Rare Diseases and some Debatable Subjects", 2nd ed. Staples, London.
Wood, P. (1946). *Brit. med. J.*, **2**, 309.

La forme variable de l'arthrite rhumatismale

RÉSUMÉ

On introduit la conception de l'arthrite rhumatismale comme réaction tissulaire à caractère multiforme. On décrit brèvement deux variétés de cette réaction tissulaire anormale: la maladie de Sjögren et le syndrome de Reiter.

A la lumière de cette théorie on décrit, à titre d'exemple, des cas de ces affections. Le premier cas, en un exemple unique en son genre, montre combien de tissus et d'organes peuvent être impliqués dans une réaction du type rhumatismal. Le deuxième cas—aujourd'hui une arthrite rhumatismale typique—avait, sans doute, débuté par le syndrome de Reiter non moins typique.

On désapprouve l'emploi de termes tels que syndrome de Felty, maladie de Sjögren ou syndrome de Reiter, menant à la ségrégation de ces affections comme si elles étaient des entités individuelles à étiologie inconnue et non des variantes du même type de réaction tissulaire.

El cuadro variable de la artritis reumatoide

SUMARIO

Se introduce el concepto de la artritis reumatoide como reacción tisular de carácter multiforme. Se describe brevemente dos variedades de esta reacción anormal de los tejidos: la enfermedad de de Sjögren y el síndrome de Reiter.

A la luz de esta teoría se describen casos ilustrativos de estas afecciones. El primer caso demuestra de manera destacada como muchos tejidos y órganos pueden estar envueltos en la reacción reumatoide. El segundo caso—que hoy día presenta un cuadro típico de artritis reumatoide—había indudablement empezado por un, no menos típico, síndrome de Reiter.

Se desaprueba el empleo de términos como síndrome de Felty, enfermedad de Sjögren o síndrome de Reiter, ya que lleva a la segregación de estas afecciones como entidades individuales de etiología desconocida, siendo éstas tan sólo variantes del mismo tipo de reacción tisular.

EFFECT OF STILL'S DISEASE ON THE HAEMOPOIETIC SYSTEM*

BY

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Recent discoveries of a possible endocrine dysfunction in rheumatoid arthritis have opened up a new line of approach and may eventually provide the key to its cause and to certain hitherto unexplained clinical features.

Rheumatoid disease in childhood has often such a dramatic onset and acute course that for a time the diagnosis may be in considerable doubt. The term " rheumatoid disease " is used advisedly, as polyarthritis may not at first be the most prominent symptom. Fever is the most striking feature at this stage and the child appears to be quite ill with little in the way of physical signs except possibly a macular rash (see Figs 1 and 2).

Blood Picture in Still's Disease

The blood picture, however, is typical: a marked leucocytosis in the region of 17,000 to 30,000 white blood cells per c.mm., and pronounced neutrophilia up to 80 or 90 per cent. Sometimes myelocytes spill over into the peripheral blood field. This leucocytosis may be maintained for some months, but often for a shorter period and in the course of a few weeks the number of white cells returns to normal (see Table, overleaf). Thereafter leucocytosis is seldom repeated, and then only in association with an acute relapse (Schlesinger, 1949).

A polymorphonuclear leucocytosis of this order with high fever naturally suggests an infection of some severity, but repeated and extensive search has never revealed any localized or general infection. Nor have any of the known antibiotics any beneficial effect whatever, and the patient drifts gradually or rapidly into the succeeding and more arthritic form of his disorder. The fever ceases and the leucocytosis disappears. Thereafter the blood picture shows little beyond a persistent moderate degree of anaemia and not infrequently a slight relative lymphocytosis.

On rare occasions the disease takes what can only be described as a rapidly malignant and fatal course. This usually occurs after the malady has become well established and is associated with a severe leucopenia with the white cells in the region of 1,500 to 3,000 per c.mm. Both neutrophils and lymphocytes are equally

* From a paper presented at the Annual General Meeting of the British Branch of the European League against Rheumatism on July 5, 1951.

FIGS 1 and 2.—Widespread raised macular rash also involving the face, in a case of Still's disease in a girl of 5½ years.

TABLE

MAIN POINTS OF INTEREST INCLUDING INITIAL LEUCOCYTOSIS IN NINETEEN CASES OF STILL'S DISEASE

Case No.	Sex	Age at Onset	Rash	Spleen	Liver	Jaundice	Initial Leucocytosis W.B.C. per c.mm.	Later Leucopenia	Pericarditis	Fever		Result
										Irregularly continuous	Periodic	
1	M	10/12	+	±	++	Slight	18,000 *P.67	1,500 *P.15 †L.85	Post mortem	+	±	Death
2	M	$2\frac{4}{12}$	+	±	—	—	24,000 P.84	—	—	+	—	Arthritis ambulant
3	F	$6\frac{8}{12}$	+	+	—	—	31,000 P.92	—	—		+	Complete recovery
4	M	$10\frac{6}{12}$	—	—	—	—	17,000 P.72	—	—	+——➤±		Arthritis
5	M	$5\frac{2}{12}$	+	—	—	—	22,000 P.78	—	—		+	Recovery
6	M	3	—	—	—	—	14,400 P.66	2,900 P.53 L.44	Post mortem	Terminal		Death
7	M	6	+	—	—		22,800 P.77	—	+		+	Arthritis
8	M	$7\frac{6}{12}$	+	—	—	—	20,000 P.80	—	—	+——➤+		Migratory arthritis
9	M	2	+	—	—	—	29,000 P.82	—	—		+	Death (*gold*)
10	M	$4\frac{3}{12}$	+	+	+	—	12,700 P.84	—	—	+——➤+		Migratory arthritis
11	M	$2\frac{7}{12}$	+	++	+++	Slight	19,200 P.57	—	—	+——➤+		No arthritis Hepatic cirrhosis
12	M	6	+	+	+ later	+	21,200 P.82	—	—		+	Slight arthritis dementia
13	F	$3\frac{9}{12}$	+ later	+	+	—	Normal	—	? (Pleurisy)	+◄——	——+	Arthritis
14	M	9/12	—	+ later	+ later	—	19,900 P.75	—	? (Pleurisy)	+◄——	——+	Severe arthritis
15	F	$2\frac{2}{12}$	+	+ later	+ later	+	28,200	3,400 P.71 L.24	+		+	Slight arthritis. Recovery from leucopenia
16	F	9	—	±	+	—	17,500 P.72	—	—	+◄—— ——➤+		Severe arthritis
17	M	4	+	+ later	—	—	22,600 P.87	—	+	+——➤+		Arthritis ambulant
18	M	5	+	+	+ later	—	16,500		+	+◄——	——+	Recovery
19	F	3	+	—	—	—	13,900 P.76	—	—	±		Arthritis

* Polymorphs per cent. † Lymphocytes per cent.

involved, but agranulocytosis with a relative lymphocytosis has been observed. These cases are exceptional, but nevertheless do occur and have to be explained.

Leucopenia in rheumatoid arthritis does not necessarily follow this dramatic course; it may, in fact, last for only a short time and be followed by a return of the blood picture to normal. Collins (1937) has reported two instances in adults

with hepatosplenomegaly where the leucopenia persisted for some months without great deterioration of the patient, and the picture is, of course, typical of Felty's syndrome.

Bone Marrow

Lymphadenopathy is by no means constant during the period of leucocytosis, although it may appear later, and the state of the bone marrow is the next obvious matter for investigation.

We have made this examination by puncture in 32 children suffering from Still's disease at various phases and repeatedly in a number of them. The picture was one of general hyperplasia, particularly of the granulocyte series, which were found to be less than 45 per cent. in only three of the 32, and comprised 60 per cent. or more of the total in all the others. A left shift in the whole series was noted, with premyelocyte counts up to 20 per cent. and myelocytes up to 30 per cent. of the total marrow cells. Stimulation of the precursors of other cells was also seen, an over abundance of megakaryocytes, for instance, being not an unusual observation.

Bearing in mind the young age group of the patients, the granulocyte proportions were interpreted as hyperplasia, and the relative percentages of the more primitive of the series represent a clear left shift.

It is interesting to note that where we have been able to see the marrow during the episodes of peripheral depression (we have not yet had the opportunity of examining it in the rare extreme cases described), it has shown no change from the granulocytic hyperplasia with left shift so characteristic of Still's disease.

In fact, when trying to correlate the marrow and peripheral blood findings in the leucopenic stage it is clear that the peripheral blood is not a mirror of the marrow. One wonders if there could be some inhibiting factor present which prevents the escape of the cells formed in the marrow into the circulation.

Hormonal Effect on Blood Formation

A comparative study of the effects of stimulation and failure of the pituitary-adreno-cortical system on blood formation is interesting. The number and relative proportion of the various circulating leucocytes seem to follow a definite pattern according to changes in hormonal control. For example, adrenalectomy in certain animals and Addison's disease in man cause a fall in the total number of leucocytes and neutrophils and a relative increase in lymphocytes (Corey and Britton, 1932). Exactly the opposite happens when the adrenals are stimulated by ACTH injections or by the production of an "alarm reaction" in certain laboratory animals. Leucocytosis results, with a rise of neutrophils and a fall of lymphocytes (Harlow and Selye, 1937; Dougherty and White, 1943; Reinhardt and Li, 1945).

Somewhat similar reactions are seen in man after a single injection of ACTH: provided adrenal function is unimpaired there is an increase in neutrophils and a decrease in eosinophils and lymphocytes. Prolonged administration of ACTH provokes a more sustained and striking change, although there is an escape of

the lymphocytes after the initial depression, no doubt due to their much larger reserve depots compared to those of the eosinophils (Hills and others, 1948). But the degree of leucocytosis produced by these experiments in normal human subjects is far below that seen in the early stages of Still's disease.

How then could this be explained ? With the present belief that rheumatoid arthritis is associated with a seriously deranged endocrine system, could the leucocytosis in acute Still's disease be a desperate stimulation of a damaged organ prior to exhaustion ? The subsequent leucopenia and relative lymphocytosis, slight in most instances but extreme on rare occasions, might then be interpreted as the result of varying degrees of ultimate failure of the adreno-cortical system.

Relationship to Leukaemia

With these dramatic blood changes in mind a possible relationship between Still's disease and leukaemia is not an unreasonable suggestion, particularly as the two diseases may be indistinguishable in their early clinical course. Can, in fact, rheumatoid arthritis with leucopenia finally develop an agranulocytosis and terminate in leukaemia ? We have studied a few cases of this nature and the literature contains rare examples (Conybeare, 1936; Türk, 1938), but confirmatory evidence in our series of bone marrow punctures covering this transformation is lacking. For the moment the matter must rest there, and we agree with most authorities who believe that these unusual forms are leukaemia from the onset, their arthritic symptoms arising from subperiosteal deposits in the vicinity of joints (Taylor, 1926; Karelitz, 1927; Hunter, 1929; Poynton and Moncrieff, 1929; Seward, 1939; Smith, 1933; Sutton and Bosworth, 1934; Poynton and Lightwood, 1932).

Summary

Blood changes in Still's disease have been observed both in the peripheral blood stream and in the bone marrow, and these have been compared to those occurring with hypophyseal-adreno-cortical disturbances.

Tentative theories are advanced to explain how pronounced and sometimes serious haemopoietic derangement might be brought about in Still's disease through hormonal defect. No proof has been found that this disease can ultimately be transformed into leukaemia.

We are indebted to Dr. E. G. L. Bywaters for the photographs of the rash.

References

Collins, D. H. (1937). *Rep. chronic rheum. Dis.*, **3**, 49.
Conybeare, E. T. (1936). *Guy's Hosp. Rep.*, **86**, 343.
Corey, E. L., and Britton, S. W. (1932). *Amer. J. Physiol.*, **102**, 699.
Dougherty, T. F., and White, A. (1943). *Proc. Soc. exp. Biol., N.Y.*, **53**, 132.
Harlow, C. M., and Selye, H. (1937). *Ibid.*, **36**, 141.
Hills, A. G., Forsham, P. H., and Finch, C. A. (1948). *Blood*, **3**, 755.
Hunter, W. K. (1929). *Trans. roy. med.-chir. Soc. Glasgow*, **22**, 51.
Karelitz, S. (1927). *Amer. J. Dis. Child.*, **33**, 394.

Poynton, F. J., and Lightwood, R. (1932). *Lancet*, **1**, 1192.
——, and Moncrieff, A. (1929). *Ibid.*, **2**, 812.
Reinhardt, W. O., and Li, C. H. (1945). *Science*, **101**, 360.
Schlesinger, B. (1949). *Brit. med. J.*, **2**, 197.
Seward, B. P. (1930). *Med. J. Rec.*, **131**, 444.
Smith, C. H. (1933). *Amer. J. Dis. Child.*, **45**, 123.
Sutton, L. P., and Bosworth, O. (1934). *J. Pediat.*, **5**, 61.
Taylor, H. K. (1926). *Radiology*, **6**, 523.
Türk, E. (1938). *Arch. Kinderheilk.*, **114**, 65.

L'effet de la maladie de still sur le système hémopoïétique

RÉSUMÉ

Les altérations sanguines dans la maladie de Still furent observées aussi bien dans le courant sanguin périphérique que dans la moelle osseuse. Ces altérations furent comparées à celles survenant au cours des troubles hypophyso-corticosurrénaux.

On avance des théories tendant à expliquer comment un trouble hémopoïétique prononcé et souvent grave dans la maladie de Still peut se produire à la suite d'un dérangement hormonal. On n'a pas trouvé de preuve montrant que cette maladie puisse se transformer en leucémie.

El efecto de la enfermedad de still sobre el sistema hematopoyético

SUMARIO

Alteraciones hemáticas en la enfermedad de Still fueron observadas tanto en el torrente sanguineo periférico como en la médula ósea y fueron comparadas con las que ocurren en la disfunción hipofiso-suprarreno-cortical.

Se adelanta teorías tentativas para explicar como en la enfermedad de Still un defecto hormonal puede producir una alteración hematopoyética pronunciada y a veces grave. No se hallaron pruebas de que esta enfermedad pueda transformarse últimamente en leucemia.

HYALURONIDASE SPREAD AND THE EFFECT OF SALICYLATES IN RHEUMATIC FEVER

BY

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Since the pioneer work of Duran-Reynals in 1928 (Duran-Reynals, 1942), there has been a considerable investigation of spreading factors (Haas, 1946; Meyer, 1947) and their antagonists (Mayer and Kull, 1947; Wattenberg and Glick, 1949; Jones, 1950), concerning especially the mucolytic polysaccharide " hyaluronidase " (Hobby and others, 1941). Guerra (1946a, b) determined resistance to hyaluronidase by calculating the area of spread of intradermal weals of hyaluronidase dye combinations. Guerra and Robles Gil (1946) claimed that active and healed rheumatic fever patients have abnormal and rapid spreading reactions to testicular hyaluronidase. They suggested, therefore, that in rheumatic fever the mesenchymal tissues are especially involved, and that the rapid spread of inflammatory agents is evidence of removal of a protective ground-substance barrier. They also reported that therapeutic doses of salicylates inhibited these enzymatic spreading reactions and they concluded that the salutary effect of salicylates is mediated by this inhibition.

Although Dorfman and others (1947) corroborated the inhibitory effects of salicylates on hyaluronidase by animal experiments *in vitro* and *in vivo*, the *in vitro* inactivation of the hyaluronidase did not occur unless the concentrations of salicylates were greater than the usual therapeutic level and within the range in which salicylates denature biologically active proteins.

Harris and Friedman (1949), using haemoglobin as an indicator, were unable to demonstrate an increased susceptibility to streptococcus hyaluronidase in the tissues of rheumatic subjects. Ragan (1948), using similar techniques, was also unable to confirm Guerra's results.

Recent interest in the relationship of the hyaluronic acid-hyaluronidase system to rheumatic fever has been stimulated by four observations (Waksman, 1949):

(1) hyaluronic acid is an important constituent of connective tissue, the site of the rheumatic process;
(2) haemolytic streptococci produce hyaluronic acid and hyaluronidase;
(3) hyaluronidase allegedly causes in the skin of patients with rheumatic fever spreading reactions which are inhibited by salicylates;
(4) hyaluronic acid increases the sedimentation rate *in vivo* (in the rat) and *in vitro*, while hyaluronidase decreases the sedimentation rate *in vitro* even in the blood of rheumatic fever patients.

Since the completion of our work, Shuman (1950) has studied the problem of inhibition of hyaluronidase, using fluorescein as an indicator dye, and has reported normal spreading reactions in eight untreated acute rheumatic fever subjects, in two patients with disseminated lupus erythematosus, and in four patients with rheumatic conditions other than rheumatic fever. He showed that in patients treated with salicylates, hyaluronidase was inhibited and the disappearance of the dye delayed. He also reported that intravenous heparin appeared to inhibit the action of hyaluronidase and that anti-histaminic drugs had no effect.

Our purposes in this study were:

(1) to determine whether subjects with acute rheumatic fever or other febrile conditions have an altered resistance to the spread of hyaluronidase as compared to normal subjects,

(2) to observe the effects of salicylates on the spread of hyaluronidase weals in patients with acute rheumatic fever and in normal subjects.

Methods

One ml. of a solution of a 1 per cent. Evans blue (T1824) in saline was added to 150 turbidity reducing units of hyaluronidase.* Intradermal weals were made in the volar surface of the right forearm by injecting exactly 0·1 ml. of the hyaluronidase/Evans blue solution, using tuberculin syringes, the plungers and tips of which were treated with bisilicon petcock grease to prevent leakage and facilitate the injection of accurate amounts. A $\frac{1}{4}$-in. 27-gauge intradermal needle was used. As controls, weals were produced on the corresponding site of the left forearm, using 0·1 ml. of the 1 per cent. sterile Evans blue solution in saline. Since it was found that the maximum spread took place after 24 hrs, all measurements were made at this time interval. The area of spread was calculated as suggested by Harris and Friedman (1949). The longest axis of the spread area and its perpendicular were measured at the end of 24 hrs. Since the area of an ellipse is computed by the formula:

$$\text{Area} = \frac{\pi D d}{4}$$ (where D is the long axis, and d the perpendicular), the hyaluronidase area can be obtained by multiplying the product of the two axes by 0·785 mm. The area of spread is the hyaluronidase area minus the control area in square millimetres.

To control the joint pain in the rheumatic subjects prior to administration of salicylates, codeine was necessary on occasion. The level of salicylates in the blood was determined during the 24-hr period of spread (Brodie and others, 1944).

Material

The patients for this investigation, selected from the Children's Hospital and the adult wards of the Cook County Hospital, were Negro and white, and ranged from 5 to 43 years of age.

Group I: Sixteen subjects in various stages of acute rheumatic fever and its chronic sequelae. No salicylates or anti-rheumatic drugs were administered before or during the course of the test (Table I).

Group II: Eight subjects with acute rheumatic fever. The skin tests were performed before and repeated during the administration of salicylates. The level of blood salicylate was determined within the 24-hr test period (Brodie and others, 1944). Only typical cases of rheumatic fever were selected. Borderline cases lacking the usual criteria were rejected from the study (Table II).

Group III: 28 adult patients with a wide variety of conditions, including cases of

* Schering Corporation "Hydase".

acute rheumatoid arthritis, acute gastro-enteritis, pneumonia, active pulmonary tuberculosis, acute pelvic inflammatory disease, acute upper respiratory tract infections, and several of the collagen diseases. None of the patients in this group received salicylates before or during the test (Table III).

Group IV: Fourteen normal young adult males. The test was carried out before and repeated during the administration of therapeutic doses of salicylates. Salicylate blood levels were also obtained during the test period. To establish maximum concentration of salicylates in the tissues, the drug was given for 48 hrs before the test period as well as during the period of reaction (Table IV). Typical spreading reactions of normal young adults before the administration of salicylates are shown in Figs 1 and 2.

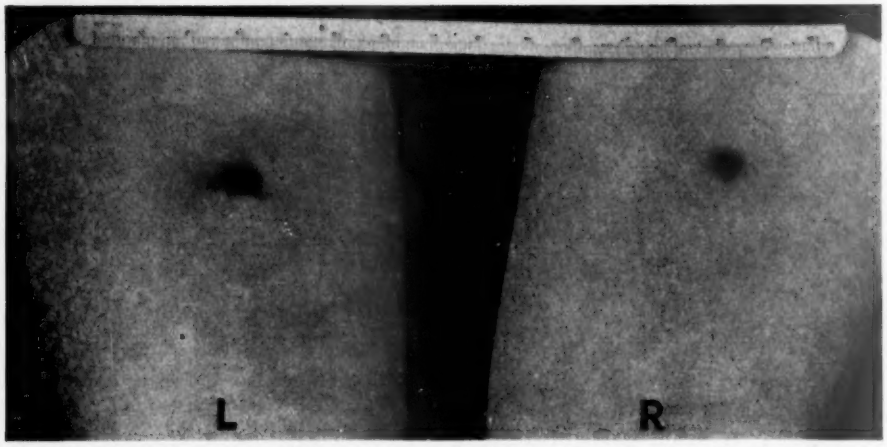

FIG. 1.—Normal young adult (not on salicylates) immediately after intradermal injection 0·1 ml. hyaluronidase/Evans blue solution (right forearm), 0·1 ml. 1 per cent. Evans blue solution in saline (left forearm).

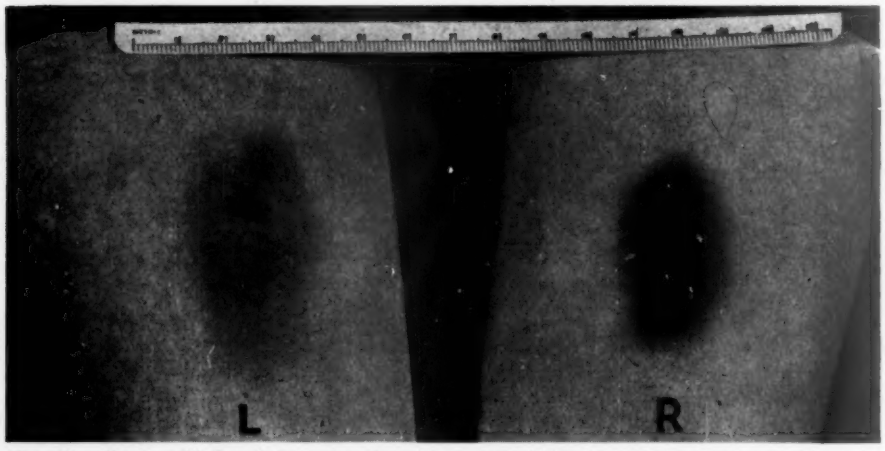

FIG. 2.—Same, 24 hrs later, showing increased diffusion of dye in larger area of spread in right forearm showing hyaluronidase effect.

Results

Our results (see Tables) are in disagreement with all those of Guerra, and corroborate the observations of Harris and Friedman (1949), Ragan (1948), and Shuman (1950), in that we were unable to discern in rheumatic fever subjects any unusual

TABLE I

AREA OF SPREAD IN UNTREATED SUBJECTS WITH ACUTE RHEUMATIC FEVER

Case No.	Age	Race	Sex	Manifestations of Rheumatic Fever	Hyaluronidase		Control		Area of Spread
					D	*d*	*D*	*d*	
1	14	C	F	Acute migratory arthritis, febrile; mitral stenosis; erythrocyte sedimentation rate—37 mm./1 hr	4·0	2·0	2·2	1·8	3·14
2	13	C	F	Acute febrile recurrent rheumatic carditis with mild congestive failure	5·0	3·8	4·0	2·5	7·07
3	20	C	F	Subsiding rheumatic carditis and arthritis; mitral configuration heart; murmurs of mitral stenosis	8·0	3·0	4·5	2·0	11·7
4	22	C	F	Acute febrile rheumatic fever with migratory arthritis	6·8	2·3	2·8	2·1	7·62
5	13	W	M	Acute rheumatic fever with migratory arthritis; systolic murmur of apex	6·0	4·0	3·5	2·3	12·5
6	43	W	M	Subsiding acute rheumatic fever; migratory arthritis; mitral stenosis	5·5	4·5	3·5	2·7	12·04
7	11	W	M	Acute rheumatic carditis with migratory polyarthritis; mitral stenosis	5·0	3·1	2·6	1·7	8·72
8	8	C	F	Haemolytic streptococcal pharyngitis; febrile; migratory arthritis; mitral insufficiency	4·3	2·2	2·7	1·8	3·82
9	11	C	M	Acute rheumatic migratory polyarthritis with carditis; mitral insufficiency; febrile	6·2	3·0	4·5	2·2	6·83
10	11	C	F	Haemolytic streptococcal pharyngitis; febrile; migratory polyarthritis; carditis; prolonged P-R interval	4·0	2·6	3·4	2·6	1·22
11	11	C	F	Recurrent rheumatic polyarthritis, acute; febrile; sedimentation rate—60 mm./1 hr; mitral insufficiency	7·0	3·0	3·0	2·0	11·5
12	14	W	F	Migratory polyarthritis; febrile—2 months, subsiding; no evidence cardiac involvement	4·0	3·0	4·0	2·5	1·57
13	7	C	M	Severe rheumatic pancarditis with pericardial effusion; acutely ill	4·5	3·7	2·5	2·0	9·2
14	8	W	F	Admitted for arrhythmia; auricular fibrillation; aortic and mitral valve involvement; febrile; subsiding carditis	4·5	3·3	3·2	2·2	6·2
15	11	C	M	Left unilateral hemi-chorea—3 weeks; no previous history or findings of rheumatic fever; afebrile	4·5	2·2	1·2	1·0	6·83
16	5	C	F	Acute febrile migratory polyarthritis; sedimentation rate—31 mm./1 hr.	5·0	2·0	3·0	2·0	3·14

or excessive spreading reactions with hyaluronidase. The administration of salicylates to rheumatic fever subjects produced no greater reduction of area of spread than was observed in the normal group. The area of spread with hyaluronidase in normal subjects was found to extend over a wide range from 7·3

TABLE II

AREA OF SPREAD IN SUBJECTS WITH ACUTE RHEUMATIC FEVER BEFORE AND DURING ADMINISTRATION OF SODIUM SALICYLATE

Case No.	Age	Race	Sex	Manifestations of Rheumatic Fever		Hyaluronidase (cm.)		Control		Area of Spread	Salicylate (g. per 48 hrs)	Blood Level (mg. per cent.)
						D	*d*	*D*	*d*			
1	6	W	F	Chronic rheumatic fever—3 mths; rheumatoid pneumonitis and carditis—3 days with early congestion fail; sedimentation rate 35 mm./hr	*B D	2·0 1·8	1·5 1·8	1·3 1·9	1·1 2·1	1·26 −0·63	8	20·0
2	10	C	F	Recurring rheumatic fever; mitral and aortic valve involvement; febrile, migratory arthritis; epistaxis—1 week before admission	B D	3·0 3·0	2·5 2·5	3·5 2·8	2·0 3·0	0·39 −0·07	7	12·2
3	15	W	F	Recurring acute rheumatic fever with migratory arthritis; mitral insufficiency; febrile; sedimentation rate 42 mm./1 hr	B D	5·0 3·5	3·2 3·0	2·7 2·3	2·0 2·0	8·32 4·63	10	29·5
4	14	W	M	Subacute rheumatic fever—1 mth; migratory arthritis; aortic and mitral valve involvement; febrile: prolonged PR interval	B D	12·0 5·0	6·0 4·0	4·0 3·8	2·5 2·4	48·67 8·56	8	23·8
5	10	C	M	Recurring acute rheumatic fever; febrile; migratory arthritis; mitral insufficiency	B D	6·0 6·0	3·0 3·5	4·5 4·5	2·5 2·5	5·26 7·62	8	27·4
6	19	C	F	Recurring rheumatic fever; febrile with migratory polyarthritis; mitral stenosis; prolonged PR interval; gallop rhythm	B D	5·5 4·0	3·2 4·0	4·0 3·0	2·8 2·2	5·03 7·38	12	29·8
7	8	C	F	Recurring acute rheumatic fever; febrile; migratory polyarthritis; tachycardia; mitral stenosis; sedimentation rate 40 mm.; epistaxis	B D	8·0 6·0	3·8 4·0	5·2 4·2	2·7 3·0	12·87 8·95	6	30·9
8	9	C	F	First attack acute rheumatic fever 4 days duration; migratory arthritis; febrile; tachycardia; sedimentation rate 34 mm./1 hr; haemostreptococci throat	B D	6·4 3·1	4·5 1·8	3·2 3·6	2·2 2·2	17·11 1·80	8	34·8

*B—before administration of salicylate.
D—during administration of salicylate.

to 53·4 sq. mm., 16 being the arithmetical average for fourteen normal subjects. With such a wide span of values in the normal group, the discernment of statistically significant areas of spread in pathological conditions is obviously inconclusive. In general, spreading reactions in the acute rheumatic fever group were not significantly different from those in the normal group. The controlled administration of therapeutic doses of salicylates to eight subjects with acute rheumatic fever (Group II) reduced the area of spread significantly in six cases, whereas in two cases the area of spread was slightly larger during salicylate administration. Spreading reactions in subjects with inflammatory conditions and collagen diseases (Group III)* were also within the normal range. This is especially noteworthy in the several patients with collagen diseases.

* Case 14 (Group III), with active hyperthyroidism, had an excessively large area of spread which may be attributed to the increased vascularity of the tissues rather than decreased resistance to hyaluronidase.

TABLE III
AREA OF SPREAD IN SUBJECTS WITH INFLAMMATORY CONDITIONS AND COLLAGEN DISEASES

Case No.	Age	Race	Sex	Diagnosis	Temperature	Hyaluronidase		Control		Area of Spread
						D	*d*	*D*	*d*	
1	20	C	F	Acute nonspecific gastro-enteritis	102° F.	4·5	3·3	3·5	2·3	5·34
2	50	W	F	Lobar pneumonia, acute, right and left lungs	101° F.	5·5	3·5	4·0	2·8	6·36
3	26	C	F	Pulmonary tuberculosis, F.A.B.	102° F.	6·0	3·0	4·0	2·5	6·28
4	32	C	F	Pulmonary tuberculosis, unilateral, F.A.	99·6° F.	6·0	2·2	3·0	2·2	5·18
5	20	C	F	Pelvic inflammatory disease, subacute; with pregnancy—3 months	Afebrile	4·2	4·0	2·7	2·2	8·56
6	56	C	F	Fever of undetermined origin; suspected periarteritis nodosa	100·2° F.	8·0	4·5	5·0	2·2	19·62
7	34	C	F	Tuberculous bronchopneumonia; RUL acute	106° F.	4·0	2·6	3·2	2·3	2·35
8	23	W	F	Chronic amoebiasis; tuberculous pleural effusion	Afebrile	5·0	3·0	3·0	2·0	7·07
9	24	C	F	Acute hepatitis	101·6° F.	2·0	2·0	3·8	2·0	−2·83
10	45	W	F	Chronic alcoholism; Laennec's cirrhosis with jaundice	Afebrile	4·5	2·5	5·0	2·5	−0·94
11	26	W	F	Obstructive jaundice	Afebrile	4·0	2·5	2·2	1·8	4·74
12	42	C	F	Acute hepatitis with jaundice	Afebrile	4·7	3·5	4·0	2·7	4·47
13	22	C	F	Acute upper respiratory tract infection	102° F.	10·9	3·8	4·4	2·6	23·55
14	36	C	F	Thyrotoxicosis, severe; diffuse enlargement of thyroid	Afebrile	9·5	4·8	5·7	2·9	32·65
15	57	W	F	Obstructive jaundice	Afebrile	5·8	3·5	2·7	2·6	10·44
16	22	C	F	Tuberculosis, pulmonary F.A. bilateral	100·8° F.	7·0	2·5	4·0	1·8	8·09
17	13	C	F	Acute tracheal bronchitis	102° F.	3·0	2·0	2·2	1·5	2·12
18	14	C	F	Infectious hepatitis with jaundice	Afebrile	5·0	4·0	3·8	2·2	0·48
19	20	Mex.	F	Alcoholic cirrhosis with jaundice	—	5·0	3·8	4·0	3·0	5·6
20	21	W	F	Chronic glomerulonephritis and severe azotaemia	—	4·7	2·6	3·5	2·5	1·72
21	19	W	F	Chronic atrophic long-standing rheumatoid arthritis	Afebrile	3·5	2·0	2·2	1·2	3·43
22	19	C	F	Acute monoarticular inflammatory arthritis, cause undetermined	—	5·0	4·5	3·0	2·0	12·95
23	39	C	F	Acute infectious arthritis	101° F.	4·5	2·2	3·0	2·0	3·06
24	26	W	F	Acute infectious arthritis	100° F.	6·8	4·7	3·7	2·5	17·83
25	20	C	F	Acute lupus erythematosus disseminatus. LE cells in marrow	103° F.	9·0	4·5	5·5	2·5	21·0
26	26	W	F	Subacute lupus erythematosus disseminatus. LE cells in marrow	Afebrile	4·5	3·8	3·0	2·3	8·0
27	41	W	F	Acute lupus erythematosus disseminatus. LE cells in marrow	—	7·0	3·5	4·5	2·5	10·36
28	19	W	F	Lupus erythematosus disseminatus, acute —terminal; LE cells in marrow	—	3·0	1·5	2·0	1·0	1·96

In ten of the fourteen normal controls (Group IV), administration of salicylates significantly reduced the area of the spreading reaction. In four of this group, the area of spread after the administration of salicylates was the same or even larger,

TABLE IV
AREA OF SPREAD BEFORE AND DURING ADMINISTRATION OF SODIUM SALICYLATE IN NORMAL CONTROLS

Case No.	Administration of Salicylate	Hyaluronidase		Control		Area of Spread	Salicylate (g./72 hrs)	Blood Level (mg. per cent.)
		D	*d*	*D*	*d*			
1	*B	15·0	6·0	7·0	3·2	53·4		
	D	13·0	5·8	8·0	4·0	34·1	9·3	22·8
2	B	7·0	4·3	3·5	3·0	15·4		
	D	4·0	3·5	3·0	2·0	6·3	22·0	38·0
3	B	7·0	3·0	4·5	2·5	7·6		
	D	4·5	2·3	3·5	1·8	3·2	19·3	22·5
4	B	6·0	5·0	4·5	2·8	13·7		
	D	5·8	4·5	4·5	3·5	8·1	12·0	9·0
5	B	7·0	5·0	4·8	3·2	15·4		
	D	6·3	3·5	4·0	2·7	8·9	22·0	26·7
6	B	6·5	5·0	4·5	3·0	14·9		
	D	6·5	4·5	5·3	4·8	3·1	29·0	33·0
7	B	9·0	5·0	4·0	2·5	27·5		
	D	7·2	4·2	4·2	3·7	11·5	14·6	21·0
8	B	5·8	4·0	4·9	3·0	6·7		
	D	6·9	3·8	4·6	3·0	9·7	22·6	25·8
9	B	9·7	4·8	6·3	4·0	16·8		
	D	7·5	5·0	4·3	3·2	18·6	24·0	37·6
10	B	7·5	4·2	3·5	3·0	16·5		
	D	5·3	3·5	3·6	2·2	8·4	30·0	31·1
11	B	6·5	4·2	4·5	4·0	7·3		
	D	6·5	4·5	5·0	2·8	12·0	30·0	24·4
12	B	7·5	5·0	5·5	3·0	16·5		
	D	4·5	3·0	3·7	2·5	3·5	30·0	30·1
13	B	7·5	3·2	4·8	3·0	7·5		
	D	7·5	4·5	4·6	2·2	8·6	23·3	21·2
14	B	8·0	3·5	4·0	4·0	9·4		
	D	7·5	4·0	4·8	3·0	12·3	20·0	23·5

*B—before administration of salicylate.
D—during administration of salicylate.

indicating that there is a considerable variation in anti-hyaluronidase factors in normal individuals. Assay of anti-hyaluronidase factors (Haas, 1946; Harris and others, 1950; Thompson and Moses, 1949) would have been highly valuable but was not obtainable in this project.

Comment

The only explanation we have to offer for the discrepancy between Guerra's results and our own is that he may have been dealing with an impure enzyme

containing other antigenic substances which produced the massive reactions he described. Also, Guerra does not report the controlled use of his material in normal individuals or in subjects with other diseases. Although our work was done with testicular hyaluronidase, Harris and also Ragan were unable to demonstrate increased susceptibility of rheumatic subjects to streptococcus hyaluronidase.

Our results confirm the observations of Dorfman and others (1947), and of Harris and others (1950) that salicylates inhibit spreading enzymes. That this inhibitory action of salicylates was not found in all subjects—normal and rheumatic—indicates that in some individuals other anti-hyaluronidase factors may be operative in varying degrees. Our results, however, do suggest that the beneficial effect of salicylates in rheumatic fever is mediated through the ground substance.

Summary

Intradermal injections of 0·1 ml. hyaluronidase/Evans blue solution, and control injections of Evans blue in saline, were made in four types of subjects:

(*a*) various phases of acute and quiescent rheumatic fever (Groups I and II),
(*b*) various inflammatory conditions,
(*c*) various collagen diseases, } (Group III)
(*d*) normal controls (Group IV).

No significant alteration in resistance to the spread of hyaluronidase could be discerned in any of the conditions studied, as shown by the size of the resulting weals.

Spreading reactions were measured before and during the administration of therapeutic doses of salicylates to a group of patients with acute rheumatic fever (Group II), and to control subjects (Group IV). Spreading reactions were found to be inhibited by salicylates in most subjects, but the effect of salicylates on this inhibition is no greater in rheumatic fever subjects than in normal subjects.

It is suggested that salicylates exert their therapeutic action directly on the ground substance by virtue of their inhibitory effect on spreading enzymes.

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REFERENCES

Brodie, B. B., Udenfriend, S., and Coburn, A. F. (1944). *J. Pharmacol.*, **80**, 114.
Dorfman, A., Reimers, E. J., and Ott, M. L. (1947). *Proc. Soc. Exp. Biol., N.Y.*, **64**, 357.
Duran-Reynals, F. (1942). *Bact. Rev.*, **6**, 197.
Guerra, F. (1946a). *Science*, **103**, 686.
—— (1946b). *J. Pharmacol.*, **87**, 193.
——, and Robles Gil, J. (1946). *Arch. Inst. cardiol. Méx.*, **16**, 293.
Haas, E. (1946). *J. biol. Chem.*, **163**, 63.
Harris, T. N., and Friedman, S. (1949). *Amer. J. Dis. Child.*, **77**, 561.
——, Harris, S., Dannenberg, A. M., and Hollander, J. L. (1950). *Ann. intern. Med.*, **32**, 917.
Hobby, G. L., Dawson, M. H., Meyer, K., and Chaffee, E. (1941). *J. exp. Med.*, **73**, 109.
Jones, E. S. (1950). *Annals of the Rheumatic Diseases*, **9**, 137.
Mayer, R. L., and Kull, F. C. (1947). *Proc. Soc. exp. Biol., N.Y.*, **66**, 392.
Meyer, K. (1947). *Physiol. Rev.*, **27**, 335.

Ragan, C. (1948). Conference on the Ground Substance of the Mesenchyme and Hyaluronidase, Dec. 3 and 4, 1948. (To be published in *Ann. N.Y. Acad. Sci.*)
Shuman, C. R. (1950). *Amer. J. med. Sci.*, **220**, 665.
Thompson, R. T., and Moses, F. E. (1949). *Science*, **110**, 70.
Waksman, B. H. (1949). *Medicine, Baltimore*, **28**, 143.
Wattenberg, L. W., and Glick, D. (1949). *J. biol. Chem.*, **179**, 1213.

La diffusion de l'hyaluronidase et l'effet des salicylates dans le rhumatisme articulaire aigu

Résumé

Des injections intradermiques de 0.1 ml. d'hyaluronidase/bleu d'Evans et des injections de contrôle de bleu d'Evans dans l'eau physiologique furent effectuées chez des sujets appartenant à un des quatre groupes suivantes:

(*a*) rhumatisme articulaire aigu à la période d'état et d'abattement (Groupes I et II),
(*b*) affections inflammatoires diverses } (Groupe III),
(*c*) maladies collagènes diverses }
(*d*) individus sains (Groupe IV).

En se basant sur les dimensions des taches produites on n'a remarqué aucune altération significative de la résistance à la diffusion de l'hyaluronidase dans les affections étudiées.

La diffusion fut mesurée avant et pendant l'administration de doses thérapeutiques de salicylates aux malades atteints de rhumatisme articulaire aigu (Groupe II) et aux témoins (Groupe IV). On a trouvé que les salicylates inhibaient la diffusion chez la plupart des sujets, mais que cette inhibition n'était pas plus accentuée chez les rhumatisants que chez les témoins.

On suggère que les salicylates exercent leur action thérapeutique directément sur la substance basique, en inhibant la diffusion de l'hyaluronidase.

La difusión de la hialuronidasa y el efecto de los salicilatos en el reumatismo articular agudo

Sumario

Inyecciones intradérmicas de 0,1 ml. de hialuronidasa/azul de Evans e inyecciones de control de azul de Evans en suero fisiológico fueron aplicadas a sujetos de cuatro grupos:

(*a*) reumatismo articular agudo en el periódo de estado y de remisión (Grupos I y II),
(*b*) varias afecciones inflamatorias } (Grupo III),
(*c*) varias enfermedades colágenas }
(*d*) individuos sanos (Grupo IV).

A juzgar por las dimensiones de las manchas producidas no hubo alteración significante de la resistencia a la difusión de la hialuronidasa en las afecciones estudiadas.

El area de la difusión fué determinada antes y después de la administración de dosis terapéuticas de salicilatos a enfermos con reumatismo articular agudo (Grupo II) y a los controles (Grupo IV). Se averiguó que los salicilatos inhibían la difusión en la mayoría de los sujetos, pero que esta inhibición no fué más acentuada en los enfermos con reumatismo que en los sanos.

Se sugiere que los salicilatos ejercen su acción terapéutica directamente sobre la substancia basal por inhibición de la difusión de la hialuronidasa.

CORTISONE, ALLERGY, AND RHEUMATIC FEVER*

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Among the infective diseases of man in which allergy is thought to play an important part, rheumatic fever is outstanding. It is associated with a haemolytic streptococcal infection of 3 to 4 weeks' duration, high antitoxin levels, and marked sensitivity to streptococcal allergens. The tissues do *not* show the " pyogenic response " commonly associated with haemolytic streptococci, but a widespread inflammation of connective tissue, which is characterized by marked oedema and collagen degeneration, and is similar to that seen in many naturally-occurring and experimentally-produced diseases associated with sensitization to various antigens, with ascorbic acid deficiency, and often with endocrine disturbance. It is irrelevant to the problem of infective allergy to discuss differences between such conditions. We are concerned with the broad analogy; diseases which resemble each other in some ways, may do so in others, so that what we learn of one may have an application in another. On this basis, we have taken certain features of rheumatic fever and studied what we think may be comparable features in the guinea-pig. We have, for convenience, selected tuberculous allergy (*not* streptococcal allergy); ascorbic acid deficiency—since it occurs both in the active stage of rheumatic fever and during convalescence; cortisone and ACTH, for obvious reasons; thyroxine, because we have a hunch that the thyroid has something to do with rheumatic fever, know that it has something to do with the adrenal cortex, believe that it has something to do with allergy, and suspect that it has something to do with ascorbic acid metabolism.

Methods

The guinea-pig is the most suitable experimental animal since, like man, it is unable to synthesize ascorbic acid. Thus, by withholding greenstuff from our animals, and feeding them only upon Bruce and Parkes (1947) pelleted diet, we could easily make them mildly deficient in ascorbic acid.

Guinea-pigs readily acquire tuberculin sensitivity, for the assay of which we had devised a simple quantitative measure based upon our finding that a linear relationship exists between the mean skin lesion diameter and the log. dose of tuberculin. A horizontal shift in the position of the dosage-response line indicates a change in sensitivity to tuberculin. The method yields results which are susceptible to statistical analysis (Long and Miles, 1950).

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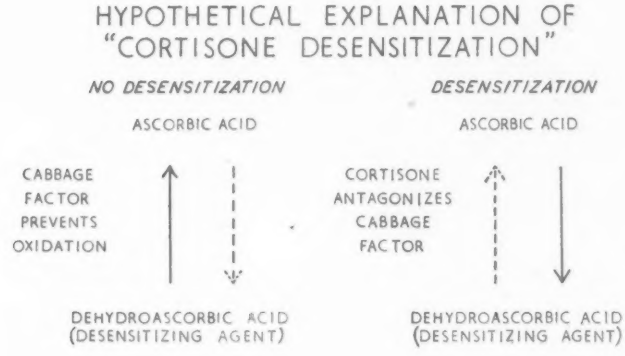
The hormones selected for test imposed technical limitations upon us. It is possible with a single dose of ACTH or cortisone to produce effects that can be observed in a short time, and approximate to a pure excess of the injected hormone. We avoided prolonged treatment with cortisone and the use of repeated injections, since it is impossible in such experiments to distinguish between effects due to cortisone, effects due to anti-cortisone compensatory mechanisms, and effects due to cortisone-induced adrenocortical deficiency resulting from ACTH inhibition. Instead, we have employed single minimal doses, which will at the same time produce maximal effects. It is impossible, however, to do the same with thyroxine because in the several days required to produce observable effects the body is probably undergoing compensatory adjustment. We gave the hormone in excess, in the hope, not of avoiding such adjustments, but of overwhelming them. Sodium thyroxine was given in sufficient quantities to prevent a 300-g. guinea-pig from gaining weight, for approximately one week before the tuberculin test. Great caution is therefore needed in interpreting thyroxine-induced effects.

Results

Initial experiments showed that ACTH and cortisone diminished sensitivity, and that thyroxine increased it, thus suggesting a simple opposition between these hormones (Long and Miles, 1950). However, we later found that propylthiouracil prevented cortisone and ACTH desensitization, which was restored by minimal doses of thyroxine, and also that cortisone and ACTH diminished the hyper-sensitivity of thyroxic animals to the same final level as that produced in non-thyroxic animals (Long and others, 1951b). We concluded that thyroxine, which in itself increases bacterial allergy, is necessary in adequate amounts for desensitization of these cabbage-fed animals by cortisone and ACTH.

The nature of this relationship is complex, but the linkage may lie in the metabolism of ascorbic acid. In the experiments so far described, the guinea-pigs were fed upon a pelleted diet with a supplement of cabbage to provide ascorbic acid. In an attempt to define the diet more strictly, we substituted ascorbic acid for cabbage, and found that it diminished sensitivity to a degree comparable to that obtained with cortisone in cabbage-fed animals; but, with cabbage omitted from the diet, neither cortisone nor ACTH influenced tuberculin sensitivity, and this was true both in guinea-pigs deficient in ascorbic acid and in guinea-pigs saturated with ascorbic acid. We concluded that there must be a factor in cabbage which influenced tuberculin sensitivity in guinea-pigs. Further experiments showed that *in all cases the diminution of sensitivity that we observed was due to ascorbic acid.* There was, moreover, a factor in cabbage which reversed the desensitizing effect of ascorbic acid; the injected cortisone, or ACTH, antagonized the cabbage effect. Cabbage may have a direct effect on ascorbic acid metabolism, but cortisone and ACTH almost certainly have not, since both are ineffective in ascorbic acid saturated animals, and their effect is not increased in cabbage-fed animals given additional ascorbic acid (Long and others, 1951a). We are attempting to isolate the cabbage factor. To speculate for a moment, the cabbage factor may be an -SH compound, possibly similar to that isolated from brassicas and other vegetables by Astwood and others (1949). Sulphydryl compounds are known to be capable

of inhibiting the enzymic oxidation of ascorbic acid *in vitro*. In support of this, we found that the -SH compound, glutathione, inhibits the desensitizing action of ascorbic acid in pellet-fed animals. It is consistent with our findings to postulate that oxidation of ascorbic acid is associated with desensitization, that cabbage contains an -SH compound which prevents oxidation in the tissues, and that cortisone antagonizes this cabbage effect and allows ascorbic acid oxidation to take place. This process may be expressed diagrammatically as follows:



We shall test this hypothesis by identifying the cabbage factor, by testing both the anti-allergic effect of oxidation products of ascorbic acid in cabbage-fed animals, and the action of cortisone on the accumulation of such products in their tissues, and by exploring the action of drugs which have an analogous effect. The reversible change ascorbic $\gtrless$ dehydroascorbic acid occurs in the body, and further oxidation results in loss of ascorbic acid, since the change is no longer reversible. In order to determine what stage in the metabolism of ascorbic acid is associated with desensitization, we tested dehydroascorbic acid and found that it desensitized in cabbage-fed animals. It appears, therefore, that as far as allergy is concerned, cortisone affects those metabolic processes that centre in the equilibrium ascorbic $\gtrless$ dehydroascorbic acid.

By investigations of this kind we hope to relate a number of definite and striking effects which we have observed, but of which the connections are at present partly speculative.

The story is, as yet, incomplete, even as far as the guinea-pig is concerned, and the facts here described apply only to guinea-pigs under the conditions of these particular experiments. To argue from animal to man by analogy amounts to little more than making a reasonable guess, and results obtained in the experimental animal may or may not hold for man. But, *if* allergy is the major aetiological factor in rheumatic fever, *if* the desensitizing action of cortisone is responsible for its clinical effectiveness in this disease, and *if* cortisone produces its effect by facilitating the formation of dehydroascorbic acid in the body, *then* dehydroascorbic acid should prove clinically effective in rheumatic fever. We can test this in man only by direct experiment. But such clinical trials could not be lightly

undertaken since dehydroascorbic acid resembles the diabetogenic drug alloxan both in its chemical structure and in many of its effects. Both are diabetogenic in the experimental animal (Patterson, 1950), and both, we have found, desensitize. We have also found that, like cortisone, alloxan is not itself anti-allergic, does not affect the anti-allergic action of ascorbic acid, antagonizes the cabbage factor, and is ineffective in propylthiouracil-fed animals. Despite the obvious dangers of using these drugs, we hope, subject to the results of full and careful toxicity trials, to give dehydroascorbic acid and alloxan a clinical trial in the treatment of rheumatic disease.

References

Astwood, E. B., Greer, M. A., and Ettlinger, M. G. (1949). *J. biol. Chem.*, **181**, 121.
Bruce, H. M., and Parkes, A. S. (1947). *J. Hyg. Camb.*, **45**, 70.
Long, D. A., and Miles, A. A. (1950). *Lancet*, **1**, 492.
——, ——, and Perry, W. L. M. (1951a). *Ibid.*, **1**, 1085.
——, ——, —— (1951b). *Ibid.*, **1**, 1392.
Patterson, J. W. (1950). *J. biol. Chem.*, **183**, 81.

Cortisone, allergie, et rhumatisme articulaire aigu

Résumé

L'allergie est presque certainement un facteur important dans l'étiologie du rhumatisme articulaire aigu. En vue de déterminer la nature des rapports entre l'allergie et les autres facteurs—hormonaux, alimentaires, et infectieux—on expérimenta sur des cobayes sensibilisés à la tuberculine.

L'étude porta sur les effets de la carence en acide ascorbique et du traitement par la thyroxine, l'ACTH, et la cortisone.

L'allergie bactérielle était augmentée par la thyroxine et diminuée par l'ACTH et la cortisone. L'acide ascorbique exerçait une action désensibilisante, similaire à celle de l'ACTH et de la cortisone, et ces hormones n'avaient pas d'effet ultérieur chez des animaux déjà désensibilisés par l'acide ascorbique.

L'action de l'acide ascorbique était empêchée par un facteur (encore inconnu) contenu dans le chou, et l'antagonisme de ce " facteur-chou " était, à son tour, supprimé par la cortisone et par l'ACTH.

On suggère que l'acide déhydroascorbique, capable de désensibiliser directement les animaux nourris de choux, est ce facteur désensibilisant.

On note la ressemblance entre l'acide déhydroascorbique et l'alloxane, dont les rapports sont indiscernables de ceux de la cortisone avec l'acide ascorbique, le "facteur-chou", et la thyroxine.

On connait le danger d'appliquer à l'homme les données de l'expérimentation animale et d'employer en clinique des substances diabétogènes telles qu'acide déhydroascorbique et l'alloxane. Toutefois, les tests de toxicité le permettant, l'auteur a l'intention de faire un essai clinique prudent dans le rhumatisme articulaire aigu.

La cortisona, la alergia, y el reumatismo articular agudo

Sumario

La alergia constituye casi ciertamente un factor importante en la etiología del reumatismo articular agudo. Con el fin de determinar la naturaleza de las relaciones entre la alergia y los demás factores—hormonales, alimenticios, e infecciosos—se ha experimentado sobre cobayos sensibilizados a la tuberculina.

Fueron estudiados los efectos de la carencia del ácido ascórbico y del tratamiento por la tiroxina, por la ACTH, y por la cortisona.

La alergia bacteriana aumentaba con la tiroxina y disminuía con la ACTH y la cortisona. El ácido ascórbico ejercía una acción desensibilizante, similar a la de la ACTH, y de la cortisona, pero en los animales ya desensibilizados por el ácido ascórbico estas hormonas quedaban sin más efecto.

La acción del ácido ascórbico era impedida por un factor (todavía desconocido) presente en la col, y el antagonismo de este " factor-col " era, a su vez, anulado por la cortisona y la ACTH.

Se sugiere que este factor desensibilizante es el ácido deshidroascórbico, el cual es capaz de desinsibilizar directamente a los animales alimentados con coles.

Se nota la semejanza entre el ácido deshidroascórbico y la alloxana, cuyas relaciones no se pueden distinguir de las de la cortisona con el ácido ascórbico, el " factor-col ", y la tiroxina.

Es obvio el peligro de aplicar al hombre los datos experimentales obtenidos en los animales y de emplear en clínica las substancias diabetógenas, tales como el ácido deshidroascórbico y la alloxana. Según los resultados de las pruebas de toxicidad el autor tiene la intención, sin embargo, de hacer una aplicación clínica cautelosa en el reumatismo articular agudo.

FURTHER OBSERVATIONS ON THE USE OF PREGNENOLONE IN RHEUMATOID ARTHRITIS

BY

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In a recent report on the treatment by pregnenolone of a group of ten cases of rheumatoid arthritis (Myers, 1951), two instances of apparent clinical improvement occurred, although there was no appreciable reduction in the erythrocyte sedimentation rate or plasma viscosity readings. Accordingly, it was decided to study the effects of pregnenolone on the serum potassium, sodium, and chlorides, as well as on the urinary 17-ketosteroid excretion and leucocyte counts, to find whether any biochemical or hormonal changes parallel the minor clinical response.

Scope of Present Investigation

Four patients were selected for the investigation. All were females aged between 20 and 41 years, and the duration of the disease varied between 6 and 12 years. They were kept under observation as in-patients of the hospital.

A brief outline of the clinical findings of each case is given. After examination, they were graded according to the system of Steinbrocker and others (1949). Two patients were given 300 mg. pregnenolone for 26 days and 100 mg. for 8 days; the other two received 300 mg. for 27 days and 100 mg. for 7 days. The drug was administered by the intramuscular and oral routes. Where the intramuscular route was employed, the pregnenolone was given in the form of a crystule suspension into the upper and outer quadrant of the buttock. The injections often caused pain and a mild inflammation at the site of the injection. In all such cases the volume of the injection was reduced or suspended entirely and the balance of the daily dose of 300 mg. given by the sublingual route.

Estimations of the erythrocyte sedimentation rate (Spa Hospitals' Method), plasma viscosity, packed-cell volume, erythrocyte, leucocyte, and eosinophil counts, differential white-cell counts, and haemoglobin estimations, were made at set intervals, before and during the administration of pregnenolone. In addition, estimations were made at intervals throughout the trial of the serum sodium, potassium, and chloride as well as the urinary excretion of 17-ketosteroids, creatinine, and uric acid. All four patients received routine physiotherapy throughout the trial period.

Case Reports

Case 1. Female, married, aged 38.—In 1944 she travelled to the West Indies, which necessitated a worrying sea trip of 3 weeks' duration *via* Greenland. About 4 months after her arrival, she developed pain and swelling in the left ankle. One month later the other ankle was similarly affected. She had " electric blanket " treatment, which gave some measure of relief. She returned to England after 7 months and, within 4 days of landing, showed signs of an acute polyarthritis involving the joints of both hands,

feet, and ankles, and the mandible. She was given a course of gold therapy in addition to physiotherapy. In December, 1944, she became pregnant and the joint condition began to retrogress. In September, 1945, the pregnancy terminated with a stillbirth. Three months later the arthritis became active in the left knee. Since then her condition had deteriorated steadily in spite of five separate courses of gold injections. At time of examination there was evidence of arthritis in both mandibular joints, as well as in the joints of the shoulders, elbows, wrists, hands, ankles, feet, and cervical spine. The onset of the disease was acute, afebrile, and mono-articular. As far back as the grandparents there was no family history of rheumatoid arthritis. Her general health was good immediately before the onset of the arthritis, but she had worried a great deal at the prospect of an ocean voyage in wartime.

Examination.—Thin type of patient, weighing 9 st. 10 lb. and taller than average. Both wrist joints enlarged, swollen, and painful, with a markedly restricted range of movements. All metacarpal and interphalangeal joints of both hands show fusiform swelling and restricted, painful movements. Fingers in the extended position. Tenderness over tarsal bones and metatarsophalangeal joints of both feet. Both ankles swollen and painful with limited range of movement. Cervical spine apparently normal. Severe arthritis in both shoulder joints, left elbow, both knees, and both hip joints. No abnormality in respiratory, cardio-vascular, or central nervous systems. Blood pressure 120/75 mm. Hg, no evidence of peripheral vascular disturbance. Palmar and plantar surfaces of limbs moist and sweaty. B.M.R. plus 15 per cent.

X-Ray Examination.—Fairly advanced arthritis of left hip joint. Acetabulum commencing to bulge. Osteoporosis not marked in the hands and wrists, but considerable destruction of many joints, particularly the proximal interphalangeal joints is seen. Astragulo-scaphoid joints particularly affected in the feet. Some rotation of vertebral bodies of lumbar spine. Lower part of sacro-iliac joints shows chronic inflammatory changes. General osteoporosis and considerable articular erosion in left knee joint. Left elbow joint shows very advanced rheumatoid arthritis with extensive damage; the right elbow appears to be normal. Both shoulder joints show evidence of osteoporosis with considerable erosion of articular surfaces of right joint.

On the eleventh day after the course of pregnenolone had been begun, the patient announced that the degree of joint stiffness had diminished appreciably, but that she still experienced severe pain in the shoulders and elbows at night. This pain was much less severe during the daytime. The knee movements were slightly increased in range and much less painful. Two days later she began to have more pain, especially in the right knee joint. By the twenty-sixth day she felt generally improved, but still had considerable pain in both shoulders and in the right leg, especially the right knee, which was aggravated by movement. Flexion of the knee joints produced crepitus. At this time the sedimentation rate showed an increase. Hip flexion produced severe pain in the groins and lower anterior abdominal muscles. In spite of these pains, she stated that her general condition had undoubtedly improved. During the previous 16 days she had observed that freckles on her skin, which were always very pale and barely discernible, had become darker; they were now much more noticeable and of a deep brownish-black colour. By the 31st day her joints were much less painful and easier to move. Before the course of pregnenolone she usually had 50 gr. aspirin a day to ease her pain, but recently she had been able to reduce this to 25 gr. a day, 10 of which she always had at night in order to ensure a " good night's rest ".

At the end of the trial period she was sleeping better and was able to turn over more easily in bed and with much less pain. She stated that her joints were better than at any time during the past 4 weeks, and there was no doubt about her being able to get about more easily than before. At the time of examination her menstrual period was 5 days overdue. She was usually very regular and always experienced articular pain during the 2 days before the onset of the menstrual period.

Case 2. Female, married, aged 23.—At age 14, she had experienced transient pains in the muscles and joints of the upper and lower limbs. Soon afterwards there were

painful swellings in the left elbow, right wrist joint, and both feet. A course of eight gold injections produced an improvement in the ankles and feet. Two additional courses of gold therapy failed to produce any further improvement in her joint condition. During the past 5 years her condition has become progressively worse. She had had two pregnancies and stated that the joint condition improved during each, only to become worse again after delivery. The onset of the disease was acute, afebrile, and polyarticular. In cold weather the hands and feet were unduly cold, the fingers and toes became white, and chilblains often followed. There was nothing of interest in her past history beyond having twice had pneumonia in childhood; the first time at 1 year, the second at 3 years. She had had two attacks of tonsillitis, the second two years before.

Examination.—Fingers of both hands show swelling of interphalangeal and metacarpo-phalangeal joints. Right wrist stiff and limited in its movements. Both ankles painful and swollen, with a diminished range of movement. Body weight 10 st.

Respiratory system: poor chest expansion, occasional cough, sometimes expectorates copious amounts of mucus. No abnormal physical signs.

Cardiovascular system: nothing abnormal detected. Blood pressure 120/80 mm. Hg. Central nervous system, digestion, and genito-urinary systems all normal. Examination of abdomen revealed nothing of interest. Tonsils small, no evidence of deep infection. B.M.R. plus 10 per cent.

X-Ray Examination.—General calcification of the bones good. Marked hypertrophic, arthritic, and erosive changes in right wrist about most of the carpal bones and the articular surface of the radius and the styloid of the ulna. No focal lesions about the joints of the hands, but joint spaces all narrowed. Appearances suggest a late hypertrophic stage of an infective type of arthritis of the wrist joint. Bones of the feet show a generalized bone rarefaction and narrowing of joint spaces. No focal erosive changes. Left elbow appears to be ankylosed. Lateral view of the right elbow shows narrowing of joint spaces, but no erosive bone changes. Left knee shows a diminution of the semilunar cartilage spaces.

After having had pregnenolone for 11 days, she stated that she felt generally improved, and that the arms and neck were less painful and stiff than before. The pain returned on the eighteenth day. The joint movements, however, remained free and she had a good range,especially in the right knee, which could be fully extended, though the movement was somewhat guarded and slow. Her general health appeared better. The pain subsided over the next few days. On the twenty-sixth day she stated that she was greatly improved in every way. The limb muscles were in excellent condition, while the joint movements were less painful and freer than at any time since she had been admitted to hospital. Most of the pain was in the right knee. By the thirty-second day she was walking better, in spite of the painful right knee. She could negotiate steps and was not so easily tired as before. Her general health had greatly improved.

Case 3. Female, unmarried, aged 20.—At age 12, she had received a severe blow on the left knee which prevented her from walking for a few weeks. Pain and swelling of both knees quickly followed. The condition soon involved the feet, hands, wrists, and elbows, and, later, the hip and shoulder joints. Gold therapy had little effect upon the joint condition. During the past five years she had had a number of natural remission phases which, however, were only partial. These were always followed by relapses and her joints have steadily deteriorated to their present state. In all, she had had four courses of gold therapy without success. The onset of the arthritis was acute, afebrile, and polyarticular. There was no history of rheumatism in her family as far back as the grandparents. There was evidence of a disturbed peripheral circulation, shown by the coldness of her fingers and toes, which readily became blue, especially in cold weather.

Examination.—Pale complexion and anxious expression, thin and underweight. Patient walks with a marked limp and some pain. Fusiform swellings of metacarpo-phalangeal joints of both hands. Similar swellings present over proximal phalangeal joints. Both wrists show a

flexion deformity with limited extension of the elbows. Knees and ankles, as well as metatarso-phalangeal joints of both feet, swollen and tender. Hips painful on movement, with gross limitation of movement, abduction 15°, flexion 20°. Limited flexion of spine. Examination of the respiratory, central nervous, and cardiovascular systems showed nothing of interest beyond a blood pressure of 140/90 mm. Hg. Digestion good, but appetite poor. Tip of spleen just palpable. Nothing abnormal in the urinary system beyond an occasional urgency of micturition. B.M.R. minus 2 per cent.

X-Ray Examination.—Carpal joints mainly involved, with erosion of left radio-carpal joint. Advanced arthritis of left elbow joint. Knee joints show generalized osteoporosis. Articular surfaces of right knee show evidence of arthritis. Acromio-clavicular arthritis on right side. Left shoulder shows osteoporosis of humeral head. Hip joints show advanced arthritis of atrophic type.

After four days of pregnenolone administration, the patient stated that her joints were not so stiff as before, but complained of dryness in the mouth during the greater part of the day. Two days later she showed signs of an intercostal fibrositis on the right side. On the eleventh day she stated that she did not feel so well. Her appetite had been deteriorating slowly since the injections were started. Because of this, the frequency of the injections was reduced to alternate days, whilst the balance of the daily dose of 300 mg. was given in the form of sublingual tablets. At this time she experienced an increasing tenderness in her feet and ankles. The injections were stopped and the whole of the 300 mg. pregnenolone administered by the sublingual route. During the next 7 days the pains became steadily worse. She believed that the pain commenced soon after the intramuscular injections were reduced and got worse after they were stopped. The pain was not so intense by the twenty-sixth day, but she still experienced a fair amount of pain when the joints were moved during examination. At this time she was walking very badly. The pain was mainly located in the dorsum of both feet, both knees, and groins, and the left shoulder. At the end of the trial her condition had not altered materially.

Case 4. Female, unmarried, aged 41.—She was well-nourished and weighed 10 st. 2 lb. In September, 1943, she experienced pain and swelling in both feet and hands. Later the knee joints became involved. A course of twelve gold injections appeared to improve her condition for a few months, when she relapsed to her former condition. In April, 1950, the knees became very swollen and she had to go to bed for 6 weeks. When she got up from her bed, she was unable to walk without crutches and she had been obliged to continue with these ever since.

Past History.—In 1932 she was found to be a diabetic and had been under treatment for the condition continuously since then. She stated that immediately before the onset of her arthritic condition, she experienced a severe mental shock over the death of a very close friend. About the same time she had an attack of chicken-pox. The onset of the arthritis was acute, febrile, and polyarticular, with no evidence of rheumatoid arthritis in her family history, or any peripheral vascular disturbances beyond persistently cold feet.

Examination.—Fusiform swellings over metacarpo-phalangeal and proximal interphalangeal joints of both hands. Both ankles and left knee swollen and tender on pressure, with limited movements. Hip joints and spine appear normal. Nothing abnormal in respiratory, cardio-vascular, or central nervous systems. Blood pressure raised to 160/95 mm. Hg. Urine contains protein and sugar in small amounts. Abdominal examination revealed nothing abnormal. B.M.R. plus 18 per cent. Serum colloidal gold reaction positive (3).

X-Ray Examination.—Left knee shows advanced degree of arthritis of infective or atrophic type, with much articular erosion, including the patellar surface. Right knee shows no abnormality. Osteoporosis in bones of both ankles, particularly the left. Tarsal bones show roughening of the surfaces in addition to slight osteoporosis.

This patient felt generally worse during the first 13 days of pregnenolone administration. Her chief complaint was of increased stiffness in all her joints and a feeling of being "run-down". By the twentieth day she became mentally depressed and experienced

increased pain in her feet and knee joints. Six days later she was still complaining of pain in her left knee, which was aggravated by weight-bearing. The feet were cold and the ankles ached when she retired to bed. There was marked oedema of both ankles, the left being worse than the right. Her general health, however, appeared to have improved. The mental depression had disappeared by the twenty-ninth day, but she still complained of pain in the left knee, especially at night. This patient showed no signs of any joint improvement during the period of the trial.

The cases were graded according to the Steinbrocker classification (1949). In no case was the functional capacity altered by pregnenolone, although some minor improvement was shown in three cases which were assessed as a Grade 3 response. No response was recorded in the fourth case.

Dosage of Pregnenolone, Erythrocyte Sedimentation Rate, and Plasma Viscosity Rates

The mode of administration of the daily dose of pregnenolone over the trial period of 34 days, and the reaction, calls for description.

Dosage.—During the first 26 or 27 days, the individual daily dose was 300 mg., but towards the end of this period, all the subjects complained of increasing stiffness in their joints. No definite cause could be assigned to this, but it was considered possible that the condition might be due to the pregnenolone. In view of this possibility, the daily dose was reduced to 100 mg. during the remaining 7 or 8 days of the trial.

Erythrocyte Sedimentation Rate.—In three cases there was a decrease in the rate after pregnenolone. Two of these were accompanied by a slight reduction in viscosity rate, while in the third case the viscosity rate was slightly raised over the same period. The fourth case showed a small increase in the erythrocyte sedimentation rate, whilst the viscosity rate was reduced slightly.

Other Findings.—No significant changes in serum sodium, potassium, or chlorides were observed throughout the trial. Erythrocyte counts, haemoglobin per cent., colour index, and packed-cell volume per cent. showed no change. Urinary 17-ketosteroid excretion was not influenced by pregnenolone.

Leucocyte Counts.—These are shown in Fig. 1. Cases 2 and 4 show a close similarity in the course followed. In each case there is a marked reduction in the number of circulating leucocytes, after the administration of pregnenolone. The results in Cases 1 and 3 are not so clear-cut; the end result shows only a small reduction in the number of leucocytes. If the final leucocyte count in Case 3 were omitted, the response would show little or no change.

Eosinophil Counts.—These are shown in Fig. 2. It is obvious that pregnenolone has no influence on the number of circulating eosinophil cells.

Estimations of Urinary Creatinine and Uric Acid.—These estimations, as well as the creatinine/uric acid ratio, are set out in the Table (overleaf). The initial determinations (24/1/51) were made on the day before the administration of pregnenolone was begun. In Cases 1 and 2 the creatinine excretion figures show an increase on the

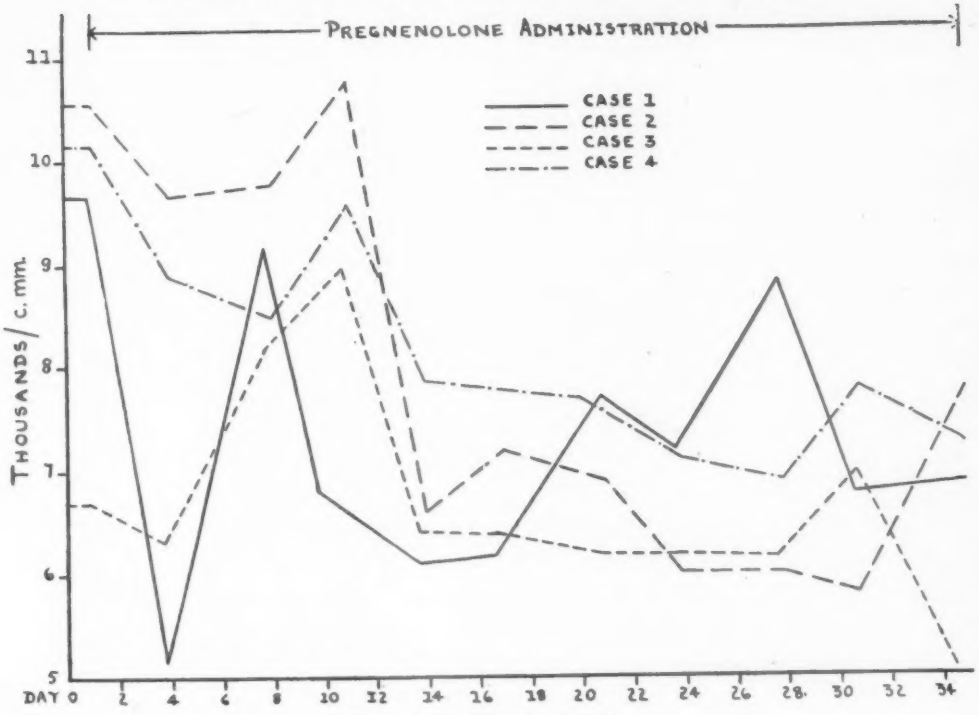

FIG. 1.—Leucocyte counts.

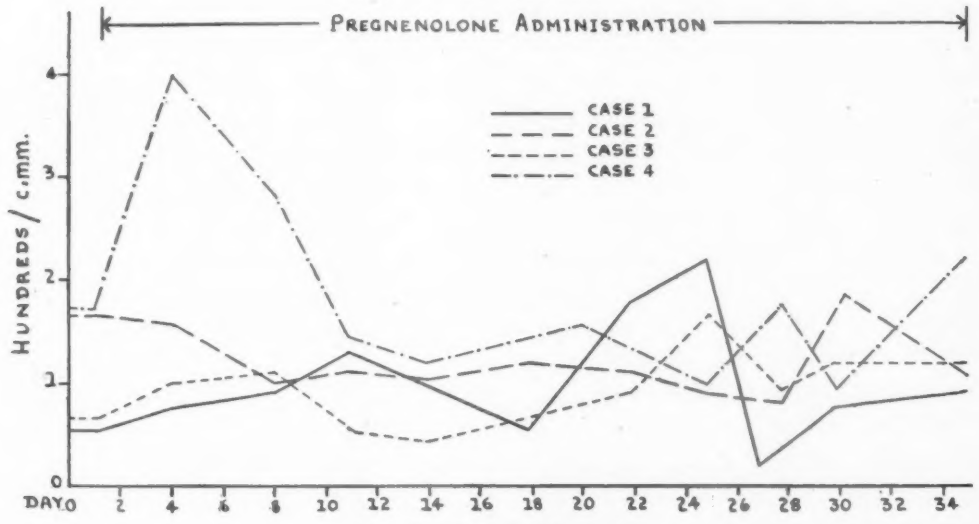

FIG. 2.—Eosinophil counts.

23rd day of pregnenolone administration (17/2/51). A similar increase was not observed in Cases 3 and 4, and it is doubtful whether this is of any significance.

Discussion

The clinical results of this investigation show that of the four patients, two (Cases 3 and 4) derived no benefit whatsoever from the administration of 300 mg.

TABLE
ESTIMATION OF URIC ACID, CREATININE, AND URIC ACID/CREATININE RATIO

Case No.	Date	Uric Acid	Creatinine	U/C Ratio
1	24/1/51	500	885	0·56
	11/2/51	745	990	0·75
	13/2/51	725	875	0·83
	17/2/51	500	1,100	0·45
	21/2/51	650	1,190	0·55
	24/2/51	645	930	0·69
2	24/1/51	390	510	0 76
	11/2/51	695	615	1·1
	13/2/51	815	700	1·16
	17/2/51	485	1,006	0 48
	21/2/51	480	715	0·67
	24/2/51	580	1,000	0·58
3	11/2/51	355	430	0·82
	13/2/51	540	605	0·89
	17/2/51	665	660	1·0
	21/2/51	490	605	0·81
	24/2/51	590	705	0·83
4	24/1/51	530	855	0·62
	11/2/51	645	585	1·1
	13/2/51	580	950	0·61
	17/2/51	600	920	0·65
	21/2/51	645	825	0·78
	24/2/51	1,120	1,260	0·88

pregnenolone daily over a period of 34 days. In neither case was there any diminution of pain or improvement in joint movements. One (Case 3) experienced a marked deterioration of appetite, whilst the other (Case 4) showed signs of mental depression from the 20th to the 29th day of the trial period.

Case 1 experienced some diminution of pain, needed fewer aspirin tablets, and was sleeping better by the 30th day. The improvement in joint movement was extremely small, but the patient was much happier and more contented than before.

Case 2 stated that she was greatly improved. Joint pain and stiffness were reduced, and walking improved so that she was better able to negotiate steps without undue fatigue.

In spite of these divergent results, most of the laboratory estimations showed little change during the period of pregnenolone administration. Of the two patients who derived no benefit from pregnenolone, one (Case 3) showed a slight reduction in the erythrocyte sedimentation rate, with no change in plasma viscosity, and the other (Case 4) showed a small increase in the erythrocyte sedimentation rate, accompanied by a correspondingly small reduction in plasma viscosity. In the only patient who experienced a marked improvement (Case 2) the erythrocyte sedimentation rate fell dramatically from 31 to 9 per cent., but the alteration in the plasma viscosity was negligible. Case 1 showed only a minor degree of improvement, and the erythrocyte sedimentation rate fell from 35 to 29 per cent., while the plasma viscosity was reduced from 21·8 to 20·6.

The leucocyte counts show that the two patients not improved by pregnenolone both showed a definite reduction in circulating leucocytes and that the course followed by each was approximately the same. On the other hand, Cases 1 and 2 showed some clinical improvement, and also show a very slight decrease in leucocytes. It is difficult to interpret these results, because if pregnenolone in any way resembled cortisone, especially in its effects on the tissues, one might have expected the greater reduction in the total leucocyte counts to have been evident in the two cases which showed clinical improvement. Thus one cannot believe that these two compounds have any similarity in their mode of physiological action.

Pregnenolone does not appear to influence serum potassium, sodium, or chlorides. Nor does it affect the creatinine/uric acid ratio or the urinary 17-ketosteroids.

Pigmentation of both skin and nails is mentioned by Thorn and others (1950) as occasionally complicating both cortisone and ACTH administration for long periods. They suggest that this may be related to interference with sulph-hydryl systems in the tissues concerned, allowing melanin deposition. In the present investigation, one patient (Case 1) showed a deepening in colour of the skin freckles, from a faint, almost imperceptible yellowish colour, to a deep brownish-black hue, almost like dark mahogany. According to the patient's own statements, this colour change, which is usually associated with melanin deposition, had never occurred to her before, not even when she lived in the bright sunshine of the West Indies. Whether there is any relationship between the pigmentary changes in the skin, described by Thorn and his co-workers, and the changes seen in our patient, it is difficult to say. In our case the deep pigmentation did not assume a general distribution over the skin surface, but only occurred where freckles had previously existed.

The results do not support the belief that pregnenolone exercises any beneficial action in rheumatoid arthritis.

Summary

(1) Four female patients suffering from rheumatoid arthritis were given a daily dose of 300 mg. pregnenolone by the intramuscular and sublingual routes for a period of 34 days.

(2) Two cases showed no improvement whatsoever; one showed a very minor clinical improvement; the fourth showed a more marked clinical improvement.

(3) Pregnenolone did not influence the serum content of sodium, potassium, or chlorides, nor had it any effect upon the creatinine/uric acid ratio.

(4) The leucocyte response to pregnenolone was not consistent. The two cases which showed no clinical improvement showed a reduction in the circulating leucocytes; the reduction in the other two cases was so small as to be negligible.

We should like to thank Messrs. Ciba Ltd., for the supply of pregnenolone, and Dr. Gerard Lorriman for his help in many ways, and we are indebted to Mr. Steel of the Royal Bath Hospital for the blood counts, and Mr. Moffett for the chemical estimations.

References

Myers, G. N. (1951). *Annals of the Rheumatic Diseases*, **10**, 32.
Steinbrocker, O. M., Traeger, C. H., and Batterman, R. C. (1949). *J. Amer. med. Ass.*, **140**, 659.
Thorn, G. W., Forsham, P. H., Frawley, T. F., Hill, S. R., Roche, M., Staehelin, D., and Wilson, D. L. (1950). *New Engl. J. Med.*, **242**, 783, 824, 865.

Nouvelles observations sur l'emploi de la pregnenolone dans le traitement de l'arthrite rhumatismale

Résumé

(1) Quatre malades atteints d'arthrite rhumatismale reçurent pendant une période de 34 jours la dose quotidienne de 300 mg. de pregnénolone par voie intramusculaire ou sublinguale.

(2) On n'observa aucune amélioration dans deux cas; il ent une très faible amélioration clinique dans un cas et une, plus prononcée, dans le quatrième.

(3) La pregnénolone ne modifia pas le taux sérique du sodium, du potassium ni des chlorures; elle n'exerça, non plus, aucun effet sur le quotient créatinine/acide urique.

(4) La réaction leucocytaire à la pregnénolone fut paradoxale: il eut une leucopénie dans les deux cas non améliorés; dans les deux autres cas la leucopénie fut si peu marquée qu'on peut la considérer comme négligeable.

Observaciones ulteriores sobre el uso de la pregnenolone en el tratamiento de la artritis reumatoide

Sumario

(1) Cuatro enfermos con artritis reumatoide recibieron durante un período de 34 días la dosis diaria de 300 mg. de pregnenolone por vía intramuscular o perlingual.

(2) En dos casos no se vió mejoría alguna; hubo poca mejoría clínica en otro y más pronunciada en el cuarto caso.

(3) La pregnenolone no cambió la cifra del sodio, del potasio o de los cloruros en el suero; no tuvo, tampoco, efecto alguno sobre el cociente creatinina/ácido úrico.

(4) La reacción leucocitaria a la pregnenolone fué paradójica: leucopenia evidente en los dos casos sin mejoría e insignificante en los demás.

ULTRASOUNDWAVE TREATMENT OF CHRONIC DISORDERS OF THE LOCOMOTOR SYSTEM

BY

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Treatment with ultrasoundwaves is the latest method of physical therapy to attract attention in many countries. Langevin and others (1923) first proved the existence of biological effects of ultrasoundwaves in experiments in which they killed small fishes. Pohlman and his co-workers (1939) used ultrasoundwaves in the treatment of sciatic pain and other neuralgias. But only since 1945 has it become possible to build and distribute ultrasoundwave apparatus so that their effects could be studied on a wider scale. These results have been acclaimed as successful, besides being subjected to severe criticism.

Definition.—The name ultrasound (U.S.) is given to a " sound " produced by more than 18,000 mechanical vibrations per sec. which is not audible to the human ear.

Production.—This high frequency can be produced with the aid of magnetic effects (Joule) by introducing a nickel rod into a magnetic field where it may vibrate at a rate of 100,000 or even 170,000 longitudinal vibrations per sec. The frequency can be further increased by making use of the piezo-electric effect (Curie). Here a quartz-crystal plate, cut at right angles to its axis, is introduced into an electrical alternating field of high frequency. The plate then vibrates at more than 300,000 vibrations per sec.

The number of vibrations depends on the thickness of the plate. For medical purposes a frequency of 800,000 vib./sec. is commonly used, and the plate is 3·6 mm. thick. Quite often therapeutic frequencies of 450,000 to 1,200,000 vib./sec. are selected (kilocycles). For experimental purposes, frequencies up to three times this therapeutic range can be achieved.

When the frequency of the electrical alternating field is made to coincide with that of the mechanical vibrations of the quartz plate, maximal vibration amplitudes can be produced which result in optimal effectiveness.

The ultrasoundwaves are conducted from the quartz plate on to a flexible metallic diaphragm, which together with the high tension cable and cooling system constitutes the " transducer head ".

Dosage.—For therapeutic use a method of dosage is essential. Apart from the frequency the effective output can be measured. This is calculated from the high-frequency energy which reaches the quartz plate.

In ultrasound apparatus of 800 kilocycles this effective output amounts to 3 to 4 watts per square centimetre (cm.^{2}). In this way, however, we can measure only the energy which reaches the plate and not that which is directed from the plate on to the body. This is limited by many factors.

Effect in Depth.—Vibration-frequency determines not only the wavelength but also the effect in depth. The higher the frequency the greater the absorption and the smaller the action in depth. Action in depth is measured with the aid of " half-value depth ", i.e. a layer of such thickness as is required to halve the ultrasoundwave intensity. In an ultrasound apparatus of 800 kilocycles this value is about 5 cm.; for this reason this frequency is most often used in therapeutic work.

Intensity diminishes geometrically. Therefore we find sufficient sound-wave action for therapeutic effects to be obtained at even greater depths. The effective maximum also depends on the size of the diaphragm, owing to " bundling " of the sound waves. Small membranes, measuring 25 mm. across, show a maximum intensity at a depth of 5 cm.; larger membranes, 40 mm. across, concentrate the radiation at 20 cm. depth (Pohlman).

Methods of Application

For the soundwave treatment of large areas with thick layers, large sound-radiation heads are to be preferred, in other cases the smaller head will be found more useful.

The " soundfield " derived from the membrane is subject to complex influences which render dosage—in any case not very reliable—inaccurate. The soundfield contains a centre of high intensity surrounded by a periphery of less intense sound waves.

The volume of sound radiation actually transmitted depends on absorption, permeability, and " beam characteristics " in the various parts of the body and on the varying density of the tissues.

Finally, the very short soundwaves lead to the formation of " standing waves " close together, so that adjacent areas of the body may receive uneven amounts of radiation.

In order to minimize this unevenness, the sound-radiation head ought to be kept constantly moving so as to make a more even distribution of sound intensity possible. The sharp demarcation between sound hills and sound dales can thus be eliminated.

If, however, the sound-head is worked by hand, there is the danger of its uneven application and of tilting. This leads to air-gaps which the radiation will have to bridge instead of entering the body directly. Like optic radiation, ultrasound radiation is reflected at a boundary surface on its path from one medium to another. Sound radiation is reflected 100 per cent. on its way from the sound membrane into the air, and is therefore altogether lost for therapeutic purposes.

To prevent this, a fluid can be inserted between the sound-head and the body surface which reduces reflection to some 30 per cent. In therapeutic work liquid

paraffin (ol. paraffini) is used which is painted on to the skin. In the larger areas of the body (shoulder, back, buttocks, abdomen) the sound-head will then glide closely and smoothly over the skin.

But in the extremities, particularly in sparely built patients, the unevenness of the surfaces would lead to gaps between sound-head and skin and much energy would be lost; such cases are treated in the bath, under water, and the sound-head is moved parallel to the extremity at a distance of 5 to 6 cm.

Accurate dosage of effective ultrasound energy is difficult, if not impossible, as we have seen when dealing with reflection, bundling, absorption, dispersion in the tissues, loss of intensity, and effective action in depth. In addition, the time factor must be taken into account. This is essential for an understanding of the therapeutic effect on the tissues, but has been neglected or altogether omitted in many published papers.

In spite of these difficulties, ultrasoundwaves are used as a therapeutic agent. Their effects have been studied, and—in part—demonstrated, in animal experiments (Barth and Bülow, 1949; Dykgraaf, 1933; Mayno, 1949; Peters, 1949; Schmitz, 1949), and in physical (Brüner and Rindfleisch, 1947; Giacomini, 1949; Pohlman, 1949), biological (Bode and Theisman, 1949; Breuning, 1949; Stuhlfauth and Wuttge, 1949), and histological (Dyroff and Horvath, 1944; Peters, 1949) investigations.

It has been found that irreversible damage to tissues results only if the usual therapeutic dosage is exceeded.

Mode of Action

As far as can be seen at present, three factors can be isolated in the as yet incompletely understood mechanism of ultrasound treatment:

(*a*) Local hyperthermy caused by absorption of energy in the tissues. With 800 kilocycles and a sound bundle of 20 mm. diameter this amounts to a rise of temperature of 5° C. at a depth of 5 cm. (Pohlman). This is a maximum which develops only at the sites of the greatest compression of the tissue under static ultrasoundwaves. Since, however, treatment with higher frequency will usually be undertaken with a mobile sound-head, local hyperthermy is so small and transient that it can be neglected. According to Krebs (1949) the average heating effect cannot be made responsible for therapeutic success, since therapeutic improvement after sound treatment was seen in cases where shortwave treatment was without effect.

(*b*) The main effect, therefore, appears to be due to mechanical factors, since the range of vibration of particles will be $4 \cdot 4$ to 10^{-6} cm. with an acceleration of $22 \cdot 4$ cm./sec. if the energy used is 800 kilocycles/sec. and 4 watts/cm.^{2} (Pohlman). With rapid acceleration and an increase of intensity there appear considerable disruptive forces in the tissues. Cell-groups are torn out of continuity and differences in density between cellular cytoplasm and nucleus lead to submicroscopical lesions within the cell. With a further increase of ultrasound energy fluid-particles may explode. The so-called cavitation is produced which consists

in the formation of cavities which are at first blown open and immediately compressed again. Since the tissues are not very compressible, an alternation of high and low pressures results which rises and falls 800,000 times per sec., from plus 3·7 to minus 3·7 atmospheres.

At a frequency of 800 kilocycles/sec., the wavelength is 2 mm. The fall of pressure occurs within half a wavelength, so that there is a momentary fall in pressure of 7·4 atmospheres per millimetre. This results in intensive micro-massage of the tissue, encourages the fluid exchange and favours intracellular metabolism. The alternating pumping action leads to hyperaemia and hyperlymphia of the tissues and improves local fluid increases and their distribution.

(*c*) There will be further molecular changes in the tissues due to colloid-osmotic and chemical reactions.

According to Pohlman (1949) it may be assumed that, with high intensities, long-chained protein molecules are being split and intermediate metabolites formed. The fluid content of certain colloidal systems is being changed, since ultrasound-waves have the power to drive fluid into shrunken tissues and thereby increase their water content and lead to softening of hardened parts of tissue.

Ultrasoundwaves, when properly applied, may diminish pain and reduce irritability of segmental nerve-endings. They may lessen the spasm of regional muscle-groups. With blood- and lymph-flow mechanically improved, chronic inflammatory products can be removed and the process of healing encouraged. At the same time the fluid content of the tissues and their permeability is increased. Sclerosed and indurated scars may become more resilient and elastic.

The hypothesis of some authors (Krebs, 1949; Pohlman, 1949), that ultrasound-waves have bactericidal powers, still awaits proof. But it is not unlikely that an increase in phagocytosis and immunobiological reactions might follow the increased blood- and lymph-supply.

Since the therapeutic effect depends largely on mechanical influences, it is obvious that ultrasoundwave therapy is contra-indicated in acute inflammatory conditions, where it would lead to reactivation and exacerbation.

Clinical Results

150 patients suffering from chronic conditions of the locomotor system were submitted to a test of the effectiveness of ultrasoundwaves. They all had had treatment with various physical methods (mud-packs, diathermy, short-wave diathermy, in some cases *x* rays) either in our department or elsewhere.

The period of treatment and follow-up extends to April, 1949. In most cases, therefore, the patients were followed up for one year.

Aseptic periostitis tibiae, "*tennis elbow*", *subdeltoid bursitis, acromial bursitis, and calcaneal spur.*—Twenty cases were treated in five to eight sessions of 5 to 8 min. duration. In 70 per cent. pain was abolished and function restored. It is important to emphasize that in such cases the intensity of ultrasound treatment must not exceed 2 to 2·5 watts/cm.^{2}. Otherwise an uncomfortable, burning,

periosteal pain will be produced. Several of these patients had previously been treated with repeated injections of Novocain without success.

Long-standing muscular rheumatism, lumbago, and resistant myalgias of the shoulder or hip.—In twenty cases the treatment proved successful, as also in cases of gluteal myalgias. The mechanical effect of ultrasound therapy is easier to understand when it is seen to be successful in this group, and also with such patients as pianists, typists, and ballet dancers, whose work may lead to chronically painful induration of muscle groups. Eight to ten treatments of about 10 min. duration using an intensity of 3·5 watts/cm.^{2} are required. Alcohol-compresses applied in the evening proved a valuable addition.

Disturbances of the peripheral circulation.—Of five patients treated, an increase in the blood-supply could be achieved in two cases of intermittent claudication. Treatments of moderate intensity (2 to 2·5 watts/cm.^{2}) were given for slowly increasing periods of from 3 to 10 min. The sound-head was moved along the course of the arteries in front of the foot, along the calf and along the anterior surface of the thigh up to the groin. The spasms in the region of the calf disappeared, the local temperature of the dorsum pedis returned to normal, and there was a measurable oscillometric improvement.

Thrombo-angiitis obliterans and Raynaud's disease.—With these cases no success was achieved. The follow-up period has been very short, and such successes as have been observed both by us and by others are unreliable. It is advisable, therefore, not to confine treatment of this group to the ultrasound therapy, but to combine with it the more usual medical and surgical procedures.

Post-traumatic joint changes after contusion or sprain.—These often appear negligible and are underrated by the doctor. Beyond some circumscribed tenderness near the insertion of a ligament no objective findings may be elicited. But the patient suffers from a considerable limitation of function against which most other methods are powerless. Here, it appears, ultrasound treatment is the method of choice. In thirty patients with pain after contusions and sprains of knee, ankle, or elbow, four to six treatments of 10 min. duration abolished all symptoms.

Arthritic changes:

Degenerative arthritis of the hip, knee, and ankle-joints.—25 patients were treated, but only at the ankle was there a favourable response after ten treatments at 4 watts/cm.^{2} for 10 to 15 min., when pain on weight bearing and movement was reduced. Arthritis of the knee responded according to whether inflammatory or degenerative changes preponderated. Only in inflammatory cases did we see a temporary improvement with painless intervals. In osteo-arthritis of the hip no success was recorded. This can be easily understood, for the often considerable fat pad in this region prevents penetration.

Inflammatory joint changes (mostly rheumatoid arthritis).—25 patients were treated; there were not only capsular changes but fully developed contractures. In all joints except the hip-joint reduction of pain and muscular spasm occurred after ten to fifteen treatments of 10 min. duration at 4 watts/cm.^{2}. Some softening

of periarticular tissues occurred, particularly near the shoulder, and we had the impression that ultrasound treatment has a softening fibrolytic effect on sclerosed tissues (Denier, 1948). The relief of painful rigidity, which is the prerequisite for mobilization and correction of deformity, can thus be achieved, but the curative effect requires passive movements and other orthopaedic measures. In this way important improvement of chronically inflamed joints can be attained, provided the patient co-operates and there is no rheumatic flare-up.

Chronic inflammatory changes of the small intervertebral joints.—Cases of arthritis of the spine, and particularly of spondylitis deformans (eighteen patients), responded very differently. Rheumatic or infective spinal arthritis can successfully be treated with short wave, but spondylitis ankylopoietica (Bechtérew) is refractory to most attempts at therapy and eventually leads to ankylosis not only of the whole spine but of other joints as well. With Hintzelmann (1949a, b), we found that ultrasound treatment gives results which are as good or better than those claimed for any other therapeutic method. It appears to cause softening of the contracted capsules and fibrotic periarticular tissues. Joints which did not yet show an osseous ankylosis gained in mobility and the excursion of the chest improved considerably. In some cases mobility improved to such an extent that the kyphotic spine straightened up. Fourteen to twenty treatments of 15 min. duration at 4 to 4·5 watts/cm.^{2} were required.

The average blood-sedimentation rate was raised by 20 to 25 mm. after the first few sittings. Two months after the end of the course the blood sedimentation rate fell below initial values. Orthopaedic measures (extension and corset) and mudbaths were also used.

Neurological Considerations.—It is important to note that in treating the spinal column the sound-head must be guided so that the soundwaves diverge from the midline, i.e. the sound-head must be tilted away from the cord. If this is not done, a temporary irritation of the cord or roots is produced. In two cases of spondylarthritis where this precaution was neglected, treatment was followed by violent spasms in the lower limbs for 3 hours with flexion in hips and knees. We had a similar experience in the region of the knee in a patient suffering from post-traumatic pain, who had violent spasms of the muscles of the calf immediately after treatment but not otherwise. The facts that these spasms always followed treatment with ultrasoundwaves and were situated in areas supplied by nerve-trunks within the treated region make it impossible to deny the causal connection between ultrasound treatment and nerve-irritation.

These findings dissuaded us, in contrast to the recommendations of Fierz and Denecke (1949), Niemöller (1949), and Pohlman (1949), from using ultrasound treatment in neurological cases, sciatic pain, and cases of neuritis. If the effects of the ultrasound, the mechanical tissue tensions, the pressure changes, and the acceleration of particles, are remembered, one cannot help fearing the danger of irreversible tissue damage in the inelastic nerve-structures. Follow-up investigations in cases of neuritis treated with ultrasound have extended over several years, but have not yet proved that no harm is being done.

Peters (1949), Schmitz (1949), and Krejci and Bejdl (1950) have confirmed our view in animal experiments. They have shown in the guinea-pig the formation of vacuoles and changes in the thickness of the myelin sheath of the sciatic nerve after ultrasound treatment with 500 kilocycles at 1·8 to 3·5 watts/cm.^{2} for 4 to 10 min. This shows the intense action of ultrasound and degeneration of nervous tissue. It would seem that these changes are due to colloid-osmotic influences.

We can, however, make use of ultrasound in neurological conditions where the consequences of degeneration do not lead to harmful effects. This applies to cases of causalgia in amputation stumps where all other conservative and surgical attempts failed. In seven cases we had a lasting success after ten treatments at 4 watts/cm.^{2}.

Conclusions

Summing up we see in ultrasound treatment a method successful in a number of disorders of the locomotor system which differs in principle from other physical modes of treatment owing to its characteristic mechanical way of action. Since dosage is still inaccurate and many of the effects are still unexplained, much further experimental and clinical work will have to be added before ultrasound can be more widely used in practice.

Only when we know more exactly the efficiency of ultrasound and its limitations, only if we can be more certain of the proper indications, shall we be able to call ultrasound therapy, alone or in combination with other methods, a valuable new asset to our therapeutic resources.

References

Barth, G., and Bülow, H. A. (1949). *Strahlentherapie*, **79**, 271.
Bode, H., and Theisman, H. (1949). *In* " Der Ultraschall in der Medizin ", p. 291. Hirzel, Zürich.
Breuning, E. (1949). *Ibid.*, p. 139.
Brüner, H., and Rindfleisch, H. (1947). *Naturwiss.*, **34**, 347.
Denier, A. (1948). *J. belge Radiol.*, **31**, 213.
Dykgraaf, S. (1933). *Z. vergl. Physiol.*, **20**, 162.
Dyroff, R., and Horvath, J. (1944). *Strahlentherapie*, **75**, 126.
Fierz, F., and Denecke, L. (1949). *Schweiz. med. Wschr.*, **79**, 1109.
Giacomini, A. (1949). *Nuovo Cim.*, N.S., **6**, 39.
Hintzelmann, U. (1949a). *Dtsch. med. Wschr.*, **74**, 869.
—— (1949b). *Schweiz. med. Wschr.*, **79**, 759.
Krebs, J. (1949). " Ultraschalltherapie ". Pagenkämpfer, Osnabrück.
Krejci, F., and Bejdl, W. (1950). *Pract. oto-rhino-laryng.*, **12**, 193.
Langevin, P., Chilowsky, C., and Tournier, M. (1923). *J. Phys. Radium*, 6 ser., **4**, 537.
Mayno, G. (1949). *In* " Der Ultraschall in der Medizin ", p. 205. Hirzel, Zürich.
Niemöller, H. K. (1949). *Dtsch. med. Wschr.*, **74**, 871.
Peters, G. (1949). *In* " Der Ultraschall in der Medizin ", p. 167. Hirzel, Zürich.
Pohlman, R. (1949). *Schweiz. med. Wschr.*, **79**, 754.
——, Richter, R., and Parow, E. (1939). *Dtsch. med. Wschr.*, **65**, 251.
Schmitz, W. (1949). *In* " Der Ultraschall in der Medizin ", p. 171. Hirzel, Zürich.
Stuhlfauth, K., and Wuttge, K. H. (1949). *Klin. Wschr.*, **27**, 662.

Additional Bibliography of Relevant Articles

Born, H. (1949). *Strahlentherapie*, **79**, 513.
Buchtala, V. (1949). *Schweiz. med. Wschr.*, **79**, 412.
Desgrez, H., and Malinvaux, J. (1949). *Paris méd.*, **39**, 354.
Dussik, K. (1949). *Wien. klin. Wschr.*, **61**, 246.
Horatz, K. (1949). *Strahlentherapie*, **79**, 635.
Schliephake, E. (1949). *Ibid.*, **79**, 613.
Ungeheuer, E. (1949). *Ibid.*, **79**, 619.

Traitement des affections chroniques du système locomoteur par des ondes ultra-sonores

RÉSUMÉ

L'auteur définit la thérapie par des ondes ultra-sonores et décrit les méthodes de production et de transmission des ondes de haute fréquence, ainsi que les moyens de les mesurer et appliquer en doses thérapeutiques efficaces.

Bien que l'action thérapeutique des ondes ultra-sonores puisse s'exercer partiellement par l'intermédiaire d'une hyperthermie locale, leur effet principal est dû à l'intense micro-massage suivi d'une hyperthermie et d'une hyperlymphie tissulaire et à des altérations moléculaires consécutives à des réactions chimiques et colloïdo-osmotiques.

L'analyse des résultats du traitement de 150 cas de différents types de rhumatisme montre qu'ils furent les meilleurs dans le rheumatisme musculaire, le lumbago et dans les myalgies de l'épaule et de la hanche.

Dans les atteintes articulaires les ondes ultra-sonores constituent un adjuvant thérapeutique utile, car elles suppriment la rigidité douloureuse, permettant ainsi la mobilisation et la correction de la position articulaire.

Le traitement est contre-indiqué en cas d'inflammation aiguë et il faut bien soigner de ne pas irriter la moelle épinière et les racines nerveuses. En cas de dégénérescence nerveuse établie, comme dans la causalgie des moignons d'amputation, des effets néfastes ne sont plus à craindre et le traitement réussit mieux.

Pour déterminer exactement la portée de la thérapie par des ondes ultra-sonores, une corroboration expérimentale plus ample est nécessaire.

El tratamiento de las afecciones crónicas del sistema locomotor por ondas ultra-sonoras

SUMARIO

Después de definir la terapia por ondas ultra-sonoras, el autor describe los métodos de producción y de transmisión de las ondas de alta frecuencia así como los medios para medir y aplicarlas en dosis terapéuticas eficaces.

Aunque la acción terapéutica de las ondas ultra-sonoras pudiera ejercerse en parte por intermedio de una hipertermia local, su efecto principal se debe a un micromasaje intensivo, seguido de hiperemia y de hiperlimfia tisular y de alteraciones moleculares consecutivas a reacciones químicas y coloido-osmóticas.

El análisis de los resultados del tratamiento de 150 casos de varios tipos de reumatismo muestra que los efectos más favorables fueron en el reumatismo muscular, en el lumbago y en las mialgias del hombro y de la cadera. En la enfermedad articular las ondas ultra-sonoras contribuyen a la recuperación porque suprimen la rigidez dolorosa y permiten la movilización y la corrección de la posición articular.

El tratamiento es contraindicado en casos de inflamación aguda y hay que evitar cuidadosamente una irritación de la médula espinosa y de las raices nerviosas. En casos de degeneración nerviosa establecida, como en la causalgia de un muñón, ya no se puede hacer daño y el tratamiento da buenos resultados.

Se necesitan más experimentos para poder determinar exactamente la posición de la terapia por ondas ultra-sonoras.

EFFECTIVENESS OF DIFFERENT FORMS OF HEATING

BY

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It is generally stated that diathermy and penetrating short-wave infra-red radiation are more effective for heating deep subcutaneous tissues than are the non-penetrating rays of long-wave infra-red or the heat derived from direct contact, but there are few experimental studies on the extent of the difference involved. We report here some observations on the temperature changes produced in the lumbar region by these different methods of heating.

Methods

Tests were made in the lumbar area of one subject on different days. The area was made flat by having the subject prone with pillows packed under the abdomen, and temperatures were measured at the centre point of the area, 2·5 cm. to the right of the second lumbar vertebral spine. Skin temperature was recorded with two copper-constantan wire thermocouples (Whyte, 1951), and subcutaneous temperatures with needle thermocouples passed vertically into the region (Whyte and Reader, 1951).

(*a*) *Short-Wave Infra-Red Radiation.*—This was supplied from a 1,000-watt tungsten filament lamp;* it was applied to a 12 × 12 cm. area in the maximum intensity which could be tolerated without being uncomfortable. The intensity was 2·5 pyrons (g. cal./sq. cm./min.), measured with the thermoradiometer of Evans and Mendelssohn (1946). Heating was continued for 18 min., by which time equilibrium was established in the region.

(*b*) *Long-Wave Infra-Red Radiation.*—This was supplied from an 800-watt Sollux dark-source element;* it was applied to the same area, giving the same sensation (1·5 pyrons intensity), until equilibrium was produced.

(*c*) *Contact Heat.*—This was applied to an area of 200 sq. cm. with a rubber-bottomed metal container (Reader, 1951) through which hot water was passed. Heat was applied for 46 min.; all tissue temperatures were steady for the last 28 min.; the sensation was of comfortable warmth. A narrow vertical channel through the centre of the container allowed of deep temperatures being recorded.

(*d*) *Ultra-Short-Wave Diathermy.*—This was supplied from an "Ultratherm" apparatus operating at a fixed wave-length of 6 m. and a frequency of 50 megacycles. Soft rubber condenser electrodes (18 × 12 cm.) were placed one over 2 cm. of felt on the right side of the abdomen and one over 1 cm. of felt on the right lumbar region. Heating was continued for 30 min. at the full output of 23 filament volts. The local sensation was of mild warmth. Skin temperature and deep temperatures were recorded

* We are indebted to Hanovia Ltd., Slough, for lending this lamp.

before heating and again within 1 min. after the heat was switched off. Thermocouples were not present during heating.

Results

The results are illustrated in the Figure. The lumbar region normally has a skin temperature of 33-34° C., while subcutaneous temperatures vary with depth, rising to a maximum of about 37·3° C. at a depth of 3 cm., beyond which they are constant. This deep temperature is probably the temperature of blood flowing into the region. When contact heat or radiant heat is applied temperatures rise highest on the skin and fall with increasing depth until the normal level is reached at 3 or 4 cm.

Short-wave infra-red produced the highest skin temperature, 44·5° C., and raised the subcutaneous temperatures more effectively than either long-wave infra-red or contact heat.

By far the most effective heating of muscle was given by the Ultratherm apparatus. The maximum temperature recorded was 40·9° C. at a depth of 15 mm., and temperatures were found to exceed 39° C. over the whole depth of 5 to 40 mm. Deep temperatures exceeded superficial temperatures. These were recorded, the more superficial ones first, within 1 min. of stopping the heating, and although the temperatures would fall in that time, the change is believed to have been small. In a large number of experiments in which the temperature changes following radiant heating were measured, the temperature at a depth of 5 mm. never fell more than 0·5° C. in the first minute.

Discussion

Several points of interest arise from these results. The first is that the effectiveness of heating is practically the same with a contact method as with radiant heat from a dark source. Both of these methods are most useful for heating skin and, although tissues to a depth of 3 or 4 cm. are warmed, the methods are of little value for raising deep temperatures much above the temperature of blood. The results in the present study are not strictly comparable, since different degrees of heat were used, but it is unlikely that the effectiveness of the methods differ to any extent, as in both cases the heat is absorbed at the surface and then spreads inwards by conduction and convection. The same considerations will apply to all forms of localized heating applied to the surface, such as hot-water bottles, hot-water, wax and other substances, and electric pads or blankets.

The second point is the superiority of the tungsten-lamp radiation over radiant heat of longer wave-lengths. This is largely attributable to the ability of short-wave infra-red radiation to penetrate skin. The maximum output of the tungsten filament lamp is in the region of the wave-length 1μ, which is the most penetrating part of the spectrum of radiant heat (Hardy and Muschenheim, 1934, 1936). The results also show that both surface and deep temperatures can be maintained at a higher level with the same degree of comfort when the tungsten lamp rather than the dark-source radiation is used. This has been confirmed

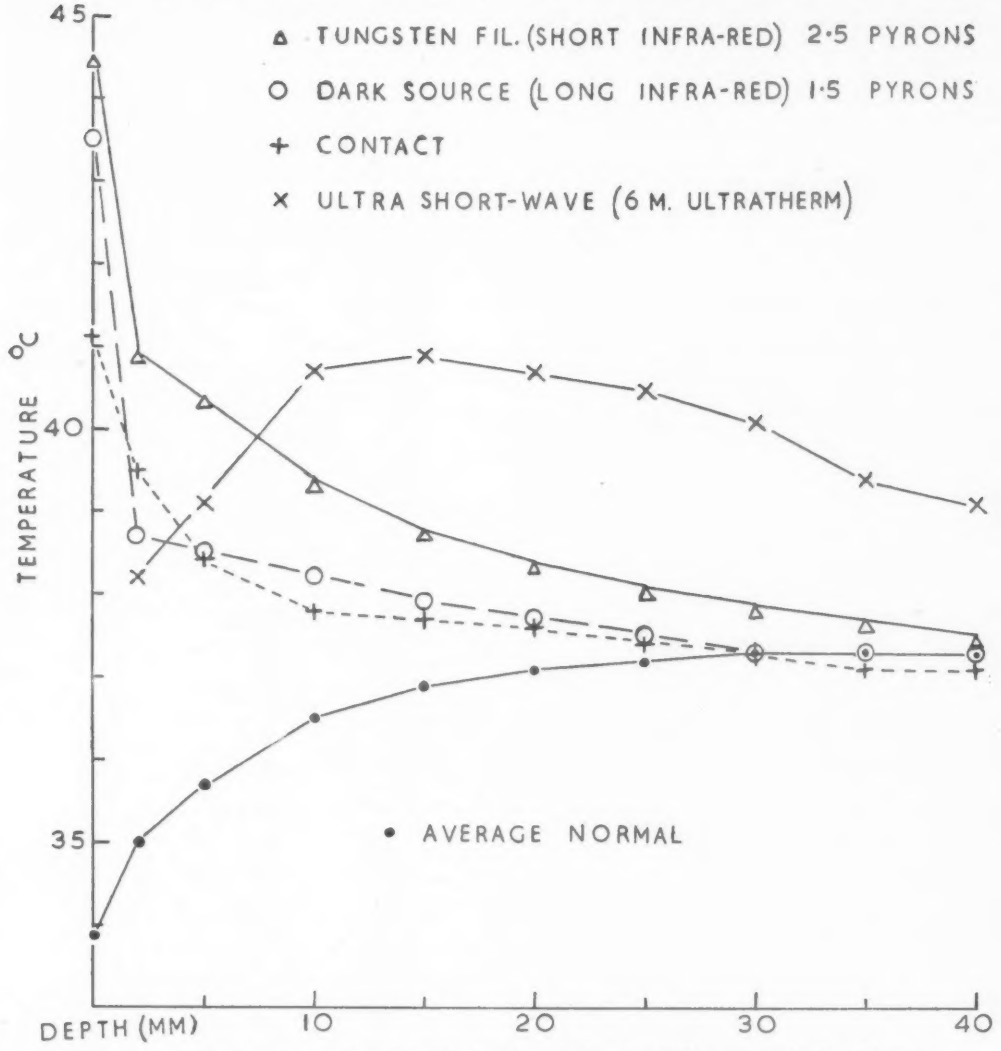

FIGURE. Temperatures produced in the lumbar region by different methods of heating.

for a large series of observations in different subjects. The difference in intensities of the two lamps is largely due to reflection by skin of a considerable proportion of the tungsten radiation.

The third point is the usefulness of diathermy for heating muscle. Grunspan (1913) showed that diathermy was superior to hot air blown on the surface, and recorded muscle temperatures of 40·5° C. after 15 min. heating. Mittelmann and others (1941) found that deep temperatures could be raised to 41° C. without discomfort and without much surface heating.

Finally, needle thermocouples, as used in the present investigation, can be recommended for recording deep temperatures and measuring the changes caused by different procedures such as the application of heat or cold. The lumbar region has many advantages for a study of this type.

Summary

Surface and deep temperature changes produced by different methods of heating in the lumbar region have been recorded.

The skin was best heated with radiation from a tungsten filament lamp and the muscle with ultra-short-wave diathermy.

The short-wave infra-red radiation from the bright tungsten lamp heated skin and deep tissues better than the long-wave infra-red radiation from a dark source.

The changes produced by the dark source of radiation and contact heat were similar.

REFERENCES

Evans, D. S., and Mendelssohn, K. (1946). *J. sci. Instrum.*, **23**, 94.
Grunspan, M. (1913). *Rev. Chir., Paris*, **48**, 585.
Hardy, J. D., and Muschenheim, C. (1934). *J. clin. Invest.*, **13**, 817.
——, —— (1936). *Ibid.*, **15**, 1.
Mittelmann, E., Osborne, S. L., and Coulter, J. S. (1941). *Arch. phys. Ther.*, **22**, 133.
Reader, S. R. (1952). *Clin. Sci.*, **11**, pt. 1, (in the press).
Whyte, H. M. (1951). *Ibid.* **10**, 325.
——, and Reader, S. R. (1951). *J. appl. Physiol.*, **4**, (in the press).

Efficacité de différentes méthodes d'application de la chaleur

RÉSUMÉ

On enregistra les variations de la température superficielle et profonde produites dans la région lombaire par différentes méthodes de chauffage.

Le meilleur échauffement de la peau fut obtenu au moyen de l'irradiation par une lampe au filament de tungstène, tandis que celui des muscles fut obtenu par la diathermie à ondes ultra-courtes.

Les rayons infra-rouges à ondes courtes provenant d'une lampe lumineuse au tungstène chauffèrent la peau et les tissus profonds mieux que les rayons infra-rouges à grandes ondes émanant d'une source obscure.

Les altérations produites par les rayons d'une source obscure et par la chaleur de contact furent similaires.

Eficacia de varios métodos de aplicación del calor

SUMARIO

Fueron enregistradas variaciones en la temperatura superficial y profunda producidas en la región lumbar por diferentes métodos de calentamiento.

El mejor calentamiento de la piel fué obtenido mediante la irradiación procedente de una lámpara con filamento de tungsteno y el de los músculos por diatermia de onda ultracorta.

Los rayos infrarrojos de onda corta producidos por una lámpara luminosa a filamento de tungsteno calentaban la piel y los tejidos profundos mejor que los rayos infrarrojos de onda larga emanados de una fuente obscura.

Las alteraciones producidas por una fuente obscura de rayos y por el calor de contacto fueron similares.

HEBERDEN ORATION*

CORTISONE : QUESTIONS THAT CAN BE ANSWERED

Dr. E. C. Kendall, of Rochester, Minnesota, winner of last year's Nobel Prize, delivered the Heberden Oration in the presence of a distinguished company at B.M.A. House, London, on September 19, 1951. In introducing him, Sir Henry Cohen, President of the Heberden Society, said that Dr. Kendall had been a formidable figure in the world of biochemistry for nearly 40 years. It was in 1914 that he had isolated thyroxin from the thyroid, but it was within the last 15 years or so that he had laid the foundations of the work which had recently resulted in the discovery of cortisone. Four years earlier, in 1948, Dr. P. S. Hench had delivered the Heberden Oration, and had spoken of the reversibility of rheumatoid arthritis, but those who listened to him then could hardly have expected that a solution of one of the most distressing and disabling diseases could have been discovered so soon. The President then asked Dr. Kendall to take up the story.

Dr. Kendall began by saying that only the week before Dr. Hench had delivered the Heberden Oration in 1948, 100 mg. of one of the hormones of the adrenal cortex had been injected intramuscularly into a rheumatoid arthritis patient at Rochester, Minnesota. That first injection, though Dr. Hench did not know it when he delivered his lecture, had been entirely successful; the patient's pain and stiffness, which she had endured for 5 years, disappeared after a few days, and she walked out of hospital. Hench in his lecture had suggested that a substance X, probably a constituent of the body, could bring about remission of symptoms in rheumatoid arthritis, and he was searching for some clue to the nature of this substance. Cortisone appeared to be the answer to years of frustration, and yet when Hench gave his lecture in 1948 it had been necessary to refrain from any premature mention of the treatment of this single patient ! That first patient had now been followed by many thousands of others, and early misgivings had been replaced by an assurance based on knowledge that cortisone brought relief from the symptoms of rheumatoid arthritis, though it was not yet known just how this was accomplished.

Substance X had never been isolated as a chemical compound; it had been described only in terms of its physiological activity, which was related to the physiological activity induced by pregnancy and by jaundice. The relationship of this product to the adrenal cortex could now be stated in precise chemical terms, and the daily requirement of the pure crystalline compound could be expressed in milligrams.

The Orator went on to relate the work in this field of the last 10 years, and to speak more particularly of the steroids that had been separated from the adrenal gland. The production of cortisone by Merck and Co. was a distinguished contribution to medicine. The rapid decrease in the cost of cortisone to-day was an important factor in its use in clinical medicine, and still further reductions in price would be made when workers such as Sir Robert Robinson had finished investigations into new methods of production. The innermost portion of the molecule, ring C, had now come within the reach of the chemist, and new sources of starting material would soon be available.

Another fine piece of work, which had already been of help to the physiologist and

* The Oration was fully reported in *Brit. med. J.* (1952), **2**, 4743.

the clinician, was the preparation of fifty or more steroids closely related to cortisone, so that it was possible to determine the physiological significance of the various functional groups in the molecule. Chemists had also devised methods for the determination of adrenocortical steroids in blood and urine. These results had indicated the amount and distribution of the steroids in the secretion of the adrenal cortex, and the fate of cortisone after it had been administered, and had given some insight into the daily amount of cortisone that could be produced by the normal human adrenal cortex.

One of the first questions concerned the chemical specificity of the action of cortisone. Are the essential functional groups in cortisone incorporated in some other steroid which could be prepared more easily ? Or is it possible that a quite different chemical structure might be as good or better ? Some examples of this sort of juggling were encouraging, but the influence of cortisone was shown to be specific, and not shared by any other steroid except hydro-cortisone (Compound F). These appeared to be the steroids which had survived the processes of selection throughout the long ages of evolution.

Another question often asked was this: Is the effect of cortisone to be regarded as physiological or simply as a pharmacological response to a massive dose of a steroid ? A partial answer could now be given to that question. Some recent work indicated that from 30 to 60 mg. cortico-steroids might be excreted daily by a normal man, unaided by the administration of ACTH. Since the total quantity of cortisone available was the sum of the amount produced in the adrenal cortex plus the amount administered, and since the production of cortisone in the adrenal gland was suppressed by administration of the hormone, the total amount available might come within the physiological range. Certainly many patients with rheumatoid arthritis were notably relieved by a daily maintenance dose of less than 60 mg. cortisone.

The small amount of cortisone required to bring about a remission of the symptoms of rheumatoid arthritis in some patients indicated that the normal human adrenal cortex could provide the necessary amount of its hormones. It seemed probable that throughout the span of human life the adrenal cortex could provide protection during the potentially dangerous phases of a latent or sub-clinical attack of rheumatoid arthritis, and it was pertinent to inquire whether failure on the part of the anterior pituitary body or of the adrenal cortex was associated with rheumatoid arthritis symptoms. Possibly the reason why lower animals did not have rheumatoid arthritis or rheumatic fever was that they were more adequately protected by a higher concentration of the hormones of the adrenal cortex within their tissues, whereas in the evolution of man a closer adjustment of the activity of the adrenal cortex resulted in an occasional failure of this safeguard.

A few questions concerning rheumatoid arthritis could now be answered. Rheumatoid arthritis was not an endocrine disease in the usual sense of the term. No combination of over-activity or under-activity of the ductless glands appeared to be important in its aetiology. Although administration of cortisone could bring about a remission in the symptoms of rheumatoid arthritis, accompanied by a nutritional gain in weight, and suppression of synovitis, these results could not serve as a basis for the hypothesis that a deficiency of the hormones of the adrenal cortex was the *cause* of rheumatoid arthritis.

As rheumatoid arthritis did not appear to be a metabolic disease caused by a disturbance in the endocrine glands, and since there were good reasons for believing that the disease was not produced by an intra-articular bacterial infection or by a virus, the search for the nature of the causative agent had been directed to still other possibilities. A study had been made of hypersensitivity and the phenomena associated with allergens, antigens, antibodies, and the results of their interaction, but it had not been established that rheumatoid arthritis was caused by a foreign agent, such as an antigen, though it was possible that cortisone caused a remission in the symptoms of rheumatoid arthritis by protecting the tissues from such an agent. Cortisone could modify the rate of production of an antibody, or protect the tissues from the effect of the products formed by combination of the antigen with the antibody.

Clinical Results

Practically all patients who had active rheumatoid arthritis responded in some degree to the administration of cortisone, and the extent of the relief was satisfactory in a large percentage of cases. Recently a group of 100 patients with rheumatoid arthritis was treated with cortisone at the Mayo Clinic. In 73 cases cortisone was given orally from the beginning; in 27 it was given intramuscularly and then orally. Only one patient did not experience relief when cortisone was given by mouth, and he responded when it was given parenterally. The main objects of this study were to determine the dose of cortisone required to suppress the symptoms, the rate at which the initial dose could be reduced, the long-term maintenance dose, the effect of withholding cortisone, and the percentage of patients in whom side-reactions developed.

The range in the daily dose of cortisone required to suppress symptoms was from 38 to 200 mg. The symptoms of one-third of the patients were suppressed by 75 mg. or less, and 20 per cent. of the patients were relieved by a daily dose of 50 mg. From 2 days to 2 weeks was the usual period required to obtain the desired degree of suppression before reduction of the dose was started.

In passing from the suppressive to the maintenance dose, the best results were obtained when the full amount of cortisone was reduced gradually and at intervals of several days. The daily dose of cortisone could be reduced more rapidly in those patients who had responded quickly to the suppressive dose. The rapidity of the reduction was determined in each case by the patient's symptomatic response, not by the sedimentation rate or other laboratory findings.

The maintenance dose was determined by reasonable control of symptoms and side-effects; 86 per cent. of the patients were maintained on a daily dose of 75 mg. or less, and more than half received 50 mg. or less a day. The effect of withdrawal of the hormone from most of the patients could not be reported, as 89 of them were still under treatment. The symptoms returned in nine of the other eleven cases when the administration of cortisone was deliberately discontinued. One of the other two of these eleven patients had been in remission for 2 months, and the other for more than 10 months.

Side-effects developed in about half the patients; in no case did the occurrence of these effects necessitate the discontinuance of the administration of cortisone, but at times the daily dose was reduced in order to control side-effects. These side-effects were related to the size of the dose of cortisone and to the sex and age of the patient.

The symptoms associated with side-effects in 54 of the 100 cases (no symptoms were observed in the other 46) were as follows:

	Times observed
Mental stimulation	29
Changes in distribution of fat	17
Changes in metabolism of electrolites	16
Increased sweating	11
Hypertrichosis	5
Hot flushes	4
Skin rash	4
Striae	3
Ravenous appetite	3
Muscular weakness	2
Menstrual disorder	2
Aggravation of diabetes	2
Increased azotemia	2
Enlargement of parotid glands	1
Polyuria	1
Nocturia	1
Headache	1
Ecchymosis	1

In conclusion, Dr. Kendall said that the fact that rheumatic symptoms were suppressed by cortisone and returned when cortisone was withheld had provided a challenge to clinical

investigators which they expected to meet and solve with some study. At the present time many questions had been answered satisfactorily; some still remained to be answered, but the advance in understanding of rheumatoid arthritis which had come about during the past 3 years lent assurance that further research would be well repaid. In the acute phase of rheumatic fever cortisone abolished the symptoms and seemed to protect the heart from damage. The two syndromes, rheumatoid arthritis and rheumatic fever, were not far separated in their nature and in their response to cortisone. Similar comparisons held for some of the other collagen diseases. Perhaps the most hopeful aspect of the study was the wide extent of clinical medicine which was influenced by this hormone. The unexpected and far-reaching influence of cortisone on many diseases might be produced through its control of some causative agent which was common to all of them. The nature of this agent was unknown, but Dr. Kendall agreed with Pickering and Meicklejohn that the hypothesis of the adaptation syndrome of Selye was not acceptable.

" To-day it can be said that cortisone will relieve the pain and symptoms of rheumatoid arthritis and that it constitutes a life-saving measure for other syndromes, but to the clinician interested in research it will be the key which will unlock the doors of barriers and reveal secrets long hidden."

Sir Henry Cohen thanked the Orator and presented him with the medal bearing the effigy of William Heberden, patron of the Society.

Among those present at the Oration were Lord Horder, Lord Webb-Johnson, Sir Henry Dale, and Dame Hilda Lloyd.

ACTHAR CONFERENCE*

A conference was held at Harrogate, Yorks., on September 13 and 14, 1951. The following papers were presented. Brief summaries are added of those having a direct bearing on the rheumatic diseases.

First Session: Chairman, Dr. F. T. G. Prunty.

(1) DR. O. JANUS (*Manchester*) gave a paper entitled **The Basic Physiology of ACTH**, in which he compared the effect of ACTH and oral cortisone on the eosinophil count; he stated that 25 mg. ACTH had an effect on the eosinophils comparable to that of 10 million T.A.B. intravenously. He mentioned the uncertainty of response to hormone stimulation, quoting one rheumatoid case that was unaffected by ACTH but responded to cortisone, one case unresponsive to both hormones, and a third case that reacted well to ACTH, but showed only a poor response to cortisone. He then proceeded to outline the effect of ACTH on hyperaemia and skin temperature by methods previously published.

(2) DR. A. SLESSOR (*Glasgow*) discussed **The Therapy and Clinical Management of ACTH**. He summarized their effects, in suitable dosage, as:

(*i*) inhibition of fibroblasts;
(*ii*) inhibition of antigen-antibody reaction;
(*iii*) increase in capillary resistance;
(*iv*) increase in resistance to stress.

If excessive doses were given, complications were apt to occur in diabetes, tuberculosis, psychosis, cardiac failure, nephritis, and hyperpiesis.

In addition there might be DOCA, androgenic, and posterior pituitary effects. He showed slides of the many investigations that might be used to control dosage; in the subsequent discussion several speakers pointed out that in the majority of straightforward cases clinical observation, routine testing of the urine for sugar, and possibly occasional potassium estimations, were all that was required, apart from research observation.

(3) DR. J. R. FORBES (*Wrexham*) spoke on **The Gastro-Intestinal Tract**, and said that he had confirmed that ACTH produced an increase in uropepsin excretion such as that which occurred in peptic ulceration and was reduced in partial gastrectomy and pernicious anaemia. He had not observed an increase in hydrochloric acid in the stomach. Six cases of perforation or haemorrhage from gastric ulcers had been described in the literature, but in many of these it was doubtful whether ACTH had in fact been the cause.

(4) PROFESSOR F. J. NATTRASS and DR. A. L. LATNER (*Newcastle*) presented a paper on **The Use of ACTH in Asthma.**

* The Conference was organized by Armour and Company Ltd., London, E.C.1.

(5) Dr. D. V. Hubble (*Derby*) spoke on **The Intravenous Treatment of Acute Dermatomyositis by ACTH.** He described in detail a severe case which was at first treated with 12·5 mg. 6-hourly with some improvement, but with persistence of fever. He had then instituted an intravenous drip for 8 hours each day for 10 days with 20 mg. daily, and then for 10 days with 10 mg. daily. At this stage the sedimentation rate and temperature rose. He had then raised the dose to 50 mg., but the patient complained of severe headache, the eosinophil count rose, and the heart dilated, but the electrocardiogram remained normal. On cessation of therapy there was a marked diuresis and the heart began to return to normal dimensions. He felt these phenomena were due to a combination of water retention and possibly sensitization to ACTH.

In the discussion, Dr. Latner suggested that the eosinophil escape might be due to the body running short of some substance produced by the ACTH which was responsible for the eosinopenia. Dr. Sevitt thought that the eosinophil cells themselves might become resistant to ACTH. Dr. Prunty and Dr. Bywaters produced evidence that one batch of ACTH had been below normal strength (said to be one-seventh strength). This was later confirmed by Dr. H. E. Cluxton, the representative of ACTHAR, who said that in America this batch had been recalled.

Commenting on the morning's papers as a whole, Dr. Cluxton made the following suggestions:

(*i*) that in using ACTH it was always advisable to restrict salt;
(*ii*) that what happens in the cell is not always reflected in the blood stream, for possibly the electrocardiogram increase in QT interval and depression of T wave might mean more than a potassium estimation;
(*iii*) that the therapy was suppressive and must be combined with other treatment;
(*iv*) that psychoses could be often cured by intravenous potassium chloride;
(*v*) that in cases of sensitivity it was possible to switch from hog to ox pituitary extract.

Second Session: Chairman, Mr. J. M. Johnston.

(1) Dr. Dudley Hart (*London*) opened with a paper on **Hypo-(Anterior) Pituitarism.**

(2) Dr. E. G. L. Bywaters (*Taplow*) discussed **The Effect of ACTH in Rheumatic Fever.** He showed how this hormone blanketed symptoms, much as was the case with aspirin, but heart lesions did not seem to be affected. He quoted one case in which pericarditis began while the patient was under full doses of ACTH. Again rheumatic rashes were often not influenced and biopsies of nodules showed little change after ACTH administration.

In a series of 46 cases, divided by random sampling for treatment with ACTH, cortisone, and aspirin, there was little difference in the numbers uncontrolled, in prevention of murmurs, or in the relapse rate. In a series of 79 cases, the only complications were: one case of cellulitis, two of tuberculous infections, two of stomatitis, two of pigmentation, and three of water retention leading to fits. ACTH had a slight influence on the spreading effect of hyaluronidase in rheumatic fever subjects.

Dr. J. D. O. Fearnley stated that as reduction of sedimentation rate and fibrinogen level appeared to run parallel, the effect of a single injection of ACTH on the fibrinogen level in normal students had been measured. It had been shown to cause a reduction.

(3) Dr. G. D. Kersley and Dr. L. Mandel (*Bath*) gave a paper on **The Comparative Effects of Hypoglycaemia with ACTH and Cortisone in Rheumatoid Arthritis, with an Investigation of Two Cases completely Resistant to ACTH.**

Twenty-two cases had been treated with a daily dosage of 60 mg. cortisone or 30 mg. ACTH and later hypoglycaemia, and then with hypoglycaemia and cortisone or ACTH. It was felt that hyperglycaemia probably stimulated the pituitary, and produced a clinical

effect equivalent to 40 mg. ACTH. Seventeen of the 22 cases showed the best clinical result with the combined treatment.

Two cases completely clinically resistant to ACTH up to a dose of 400 mg. in a day were described. Neither responded to 100 mg. ACTH intravenously, and one did not respond to 500 mg. cortisone, though in the other the cortisone appeared to act satisfactorily. Neither case appeared to suffer from adrenal insufficiency, and the Thorn and Keppler tests were normal. Some metabolic observations were recorded.

As there was complete absence of correlation between clinical response and the Thorn test, it was suggested that the fraction of ACTH responsible for the remission obtained in the majority of cases of rheumatoid arthritis was distinct from that causing the reduction in circulating eosinophils of the blood. This seemed to accord with the recent work of Young on the ascorbic acid depleting fraction and adrenal weight increasing fraction of ACTH.

Dr. J. J. R. Duthie doubted whether hypoglycaemia acted directly on the anterior pituitary. Dr. Long suggested that the failure of the two cases to respond to ACTH might be due to ascorbic acid or thyroxin deficiency.

Third Session: Chairman, Dr. W. S. C. Copeman.

(1) PROFESSOR L. J. WITTS (*Oxford*) discussed **The Effect of ACTH on Blood Diseases,** saying that the results had not been dramatic.

In the subsequent discussion several speakers said they were not impressed with the effect of ACTH or cortisone on the anaemia of rheumatoid arthritis.

(2) DR. J. J. R. DUTHIE and DR. H. N. ROBSON (*Edinburgh*) presented a paper on **The Relationship between Capillary Resistance and Adreno-Cortical Activity**. They showed a series of slides demonstrating a parallel response in increase in capillary resistance, eosinopenia and clinical benefit with both ACTH and cortisone, although more slowly with the latter, and a fall in resistance with 20 mg. desoxycorticosterone acetate (DOCA). In a case of Simmond's disease, the capillary resistance increased with a small dose of either insulin (4 units) or adrenaline, more quickly than it did with ACTH (25 mg.). With progesterone, testosterone, oestrone, or pregnenolone, there was no change either in capillary resistance or in eosinophil response. They felt that estimation of increase in capillary resistance was an easy and quick method of estimating glucocorticoid effect. The apparatus used was as previously described, but must have a satisfactory exhausting mechanism, lighting, and lens.

Fourth Session: Chairman, Professor F. J. Nattrass.

(1) DR. W. WOLMAN (*Manchester*) gave a paper on **The Function of the Adrenal Glands in the Newborn**. He said that this subject had been studied by means of the eosinopenic response to ACTH in 24 full-term and twelve premature infants. Sixteen of the full-term infants and eight of the prematures had a normal adrenal response, as shown by 50 per cent. fall in eosinophils on the first day. Of the remainder, all but two had a normal response on the second day. The smallest child responded on the third day, whereas the child of a diabetic mother responded only on the seventh day. These results suggested that though in the first days of life the adrenal cortex is histologically immature, its function is normal in most full-term and premature babies on the first day of life.

(2) Dr. W. S. C. Copeman and Dr. Oswald Savage (*London*) gave a paper on **Rheumatoid Arthritis**. They reported that every case studied had responded with measurable clinical improvement, but that the lowest dose at which initial improvement had occurred was 120 mg. ACTH a day, given in four intramuscular injections. The lowest maintenance dose achieved was 40 mg./24 hrs, also in four injections, and any lowering of the number of injections had resulted in relapse at this dosage. The best method of judging the dose requirements in this disease was by a careful clinical assessment using a combination of measurements of pain, tenderness, and function. These were particularly important when judging the required maintenance dose. Using such tests it was shown that an intravenous dose of 20 mg. in an 8-hour drip gave a clinical response equal to 200 mg. by intramuscular injections. After intravenous ACTH the improvement had lasted for an average of 4 days. It had been found impossible to correlate the clinical response with pathological and biochemical changes such as a fall in eosinophils and sedimentation rate and a rise in 17-ketosteroids and corticoids; often a much higher dosage was required to obtain these changes than to achieve a clinical response. It had been found impossible to predict what dose a patient would require for either initial or maintenance dosage.

(3) Dr. H. E. Cluxton (*Chicago*) spoke on **Recent Concepts in the Use of ACTH and Cortisone**. He reviewed recent work in America with these substances, and suggested that ACTH should be used to stimulate the suprarenal when cortisone was withdrawn. During routine long-term therapy with either substance a low salt diet and the addition of 3 g. potassium a day was advisable. There was no doubt that intravenous administration resulted in a great saving of material and was becoming a feasible proposition in certain cases. Eosinophil counts were now being done only as a preliminary to treatment.

EUROPEAN LEAGUE AGAINST RHEUMATISM

SECOND EUROPEAN CONGRESS OF RHEUMATOLOGY, BARCELONA, 1951

A most successful meeting of the European League against Rheumatism was held at Barcelona on September 24-27, 1951. All the member countries were well represented, and there were also a number of visitors from the American League. Dr. W. S. C. Copeman presided. Professor A. Pedro-Pons was the Chairman of the Spanish Organizing Committee.

Papers were read simultaneously in three halls, those in the first being translated and presented in English, French, and Spanish. The names of the opening speakers at the six sessions were as follows:

(1) Ankylosing Spondylitis:

Drs J. Forestier, A. Certonciny, F. Jacqueline (*Aix-les-Bains*), and Dr. J. Rotés-Querol (*Barcelona*): Clinical, Radiological, and Therapeutical Aspects.
Dr. H. van Swaay (*Leyden, Holland*): Pathology.
24 other papers followed.

(2) Ultrasoundwave Therapy:

Prof. A. Böni (*Zürich, Switzerland*): The Treatment of Rheumatic Diseases with Ultrasonics.
Prof. K. Matthes (*Erlangen, Germany*): Supersonic Waves.
Sixteen other papers followed.

(3) Endocrine Aspects of Rheumatism:

Drs C. Hamburger, M. Sprechler, K. Brochner-Mortensen, and A. Videbaek (*Copenhagen*): Problems related to the Administration of ACTH.
Prof. G. Edström (*Lund, Sweden*): Pituitary Gland Implantations.
Dr. C. Slocumb (*Rochester, Minn.*): Clinical Use of Cortisone and ACTH.
49 other papers followed.

(4) Non-Articular Rheumatism:

Drs W. S. C. Copeman and R. M. Mason (*London*): Non-Articular Rheumatism and the "Water-Retention Syndrome".
Prof. K. Gotsch (*Graz, Austria*): Rheumatism and the Vascular System.
21 other papers followed.

(5) Rheumatic Diseases associated with Brucellar Infection.

Prof. A. Robecchi (*Turin, Italy*): Brucellar Arthropathies.
Dr. R. Cirera-Voltá (*Barcelona, Spain*): Primary Brucellosis of the Locomotor System.
Prof. A. Pedro-Pons, and Drs P. Barceló, E. Batalla Boixet, J. M. Vilaseca, and J. Rotés-Querol (*Barcelona, Spain*): Osseous and Articular Manifestations of Brucellosis.
Eleven other papers followed.

(6) The final session comprised 74 papers on miscellaneous subjects.

The whole congress was excellently organized both technically and socially by the Spanish Committee, and the final ceremony was a grand banquet at which certificates

of Honorary Membership of the Spanish Rheumatological Association were presented to the following:

Dr. Walter Bauer (*Boston, Mass.*)
Dr. Guido Costa Bertani (*Buenos Aires*)
Prof. A. Böni (*Zürich, Switzerland*)
Dr. J. van Breemen (*Amsterdam, Holland*)
Dr. W. S. C. Copeman (*London*)
Dr. Florent Coste (*Paris*)
Dr. Gunnar Edström (*Lund, Sweden*)
Dr. Jacques Forestier (*Aix-les-Bains, France*)
Dr. Karl Gotsch (*Graz, Austria*)
Dr. Philip S. Hench (*Rochester, Minn.*)
Dr. Fernando Herrera Ramos (*Montevideo*)
Lord Horder (*London*)
Dr. Ejnar Jarløv (*Copenhagen*)
Dr. Gunnar Kahlmeter (*Stockholm*)
Dr. G. D. Kersley (*Bath, England*)
Dr. L. Michotte (*Brussels*)
Dr. Anibal Ruiz Moreno (*Buenos Aires*)
Dr. Louis von Pap (*Lisbon*)
Dr. Alessandro Robecchi (*Turin, Italy*)
Dr. Rudolf Schoen (*Göttingen, Germany*)
Dr. S. de Sèze (*Paris*)
Dr. Robert M. Stecher (*Cleveland, Ohio*)
Dr. Manuel Assuncao Teixeira (*Lisbon*)
Dr. Mathieu-Pierre Weil (*Paris*)
Dr. Henry P. Wright (*Montreal, Canada*)

The next meeting of the whole League has been fixed for August 24-29, 1953, at Geneva and Zürich, and in 1955 there will be a meeting in Holland.

AMERICAN RHEUMATISM ASSOCIATION

PROCEEDINGS OF THE ANNUAL MEETING, 1951

The annual meeting of the American Rheumatism Association was held at Atlantic City, New Jersey, on June 8 and 9, 1951. The presidential address was delivered by Dr. Otto Steinbrocker of New York. Abstracts of the twenty-three papers and summaries of the discussions thereon are printed below, together with the final panel discussion on " Difficulties and Complications in the Therapeutic Use of ACTH and Adrenocortical Steroids in the Rheumatic Diseases ".

Pleuropneumonia-like Organisms and their Possible Significance in Collagenous Diseases.

By RUTH H. WICHELHAUSEN, THOMAS MCP. BROWN, LUCILLE B. ROBINSON, and WILLIAM R. MERCHANT, *Washington, D.C.*

If the hypothesis that hypersensitivity phenomena are basic in the pathogenesis of collagenous diseases is accepted, the presence of an antigen, the nature of which remains to be determined, must be postulated.

Pleuropneumonia-like organisms have been implicated in rheumatic diseases. Their significance as possible antigens in collagenous disease hypersensitivity states is at present under investigation.

The unique properties of human " L " organisms would satisfy the criteria of a persistent living antigen, invisible in tissues or invaded cells. These properties also preclude their direct demonstration as aetiological agents.

In vitro studies on 28 strains of human " L " organisms reveal marked differences in sensitivity to antibiotics, myochrysine, and nitrogen mustard.

Preliminary studies indicate that antibiotics effective *in vitro* are also effective *in vivo*. This is manifested by disappearance of demonstrable " L " organisms during administration of aureomycin, chloramphenicol, or terramycin, and by transient exacerbation of clinical symptoms of collagenous diseases. The severity of this reaction parallels the *in vitro* effectiveness of antibiotics. It can be graded by dosage or route of administration (oral or intravenous). The exacerbation is not due to drug hypersensitivity. It may represent tissue response to antigen release, induced by antibiotics. It can be modified by administration of agents interfering with hypersensitivity reactions.

Discussion.—DR. BROWN: During the past few years many new and hopeful remedies for arthritis have been announced, but after clinical trial and prolonged treatment, each has finally been proven either limited or useless in providing persistent, adequate control of rheumatic diseases in general. The practising physician has encountered patient disappointment and medical uncertainty on account of these failures.

We have long believed that lasting benefit would be possible only when there was a thorough understanding of the basic mechanism operating in collagen diseases in general. To date there has been no real understanding of the mechanism.

To-day we have proposed a new total concept of this mechanism, based on clinical and laboratory studies extending over the past 12 years. We suggested a new clinical approach in June, 1949, and the methods of management making use of it to-day are very encouraging, but we believe

that we are not yet justified in drawing conclusions regarding lasting benefit. Such conclusions must depend on a sufficient number of long-term follow-up studies. This lasting benefit, or true alteration in the course of rheumatic diseases, is of the utmost importance in the evaluation of any method of management. We take this viewpoint in spite of tremendous pressure from many sides to publicize the clinical aspects in detail at this time.

We would emphasize, therefore, that our present report is directed towards the basic mechanism in these diseases. We suggest that it would be in order for the American Rheumatism Association to go on record in discouraging publicity of any new form of treatment as such in rheumatic diseases until a number of follow-up studies of at least 2 years can be assessed. We should direct more attention towards an understanding of the mechanism of collagen diseases, for we believe that to be the only way of achieving definitive lasting benefit.

DR. MARIAN W. ROPES (*Boston, Mass.*): The evidence given by Dr. Wichelhausen of the response of these organisms *in vitro*, and probably *in vivo*, to various antibiotics is interesting. In our experience we have found that there is some control *in vitro*, and probably *in vivo*, with streptomycin, which is apparently the least effective antibiotic and not very effective in our hands. Aureomycin was possibly a little more favourable. We have not tried terramycin.

I would hesitate to accept the suggestion that pleuropneumonia-like organisms are in any way related to a basic mechanism in rheumatoid arthritis chiefly because of the danger of interpreting any response to antibiotics, such as disappearance of organisms from the genito-urinary tract or change in clinical course, as any indication of aetiological relationship of the organisms to the disease.

We have been particularly interested in the relationship of pleuropneumonia-like organisms to Reiter's syndrome, and this is a field which should be studied more completely. I shall be glad to hear further reports on the use of terramycin, which is apparently the most effective in your hands against pleuropneumonia-like organisms, in Reiter's syndrome. It seems to me rather rash to interpret the response to antibiotics as any indication of the aetiological agent.

I wonder whether any studies have been made of the serological reactions to pleuropneumonia-like organisms in these patients, whether they have shown positive reactions, and whether these reactions have been changed by treatment.

DR. WICHELHAUSEN: In answer to Dr. Ropes' question regarding serological reactions: we have no definite data on this particular problem. I think everyone who has worked with this group of organisms knows that preparation of satisfactory antigens is still a difficult procedure. But it is possible, and work in this direction should be continued and extended. As far as the relation of change of course of collagenous diseases and aetiological agent is concerned, I agree that we should not draw hasty conclusions. In our own minds the exacerbation that follows the administration of certain antibiotics has been more important than any improvement, as far as attempts to understand the basic mechanism of these diseases are concerned. These exacerbations, possibly related to the effect of antibiotics on L organisms with subsequent antigen release into a system where antibody is readily available, have occurred with great regularity.

Punch Biopsy of Synovial Membrane.* By HOWARD F. POLLEY and WILLIAM H. BICKEL, *Rochester, Minn.*

Adrenal Function and Steroid Hormone Metabolism in Health and Disease. By KONRAD DOBRINER, *New York* (by invitation).

Steroid excretion patterns in man have been studied as a means of defining the details of hormone production by the adrenals and gonads. The evidence, which correlates the metabolism of normal or abnormal adrenal hormone production in arthritis, is compared with the findings in healthy subjects and in patients with neoplastic disease. The capacity of the adrenal to respond to stimulation by ACTH, in patients with arthritis, and type and character of the response is presented. The metabolism of cortisone in an arthritic patient and the change in steroid pattern during pregnancy are correlated with the arthritic syndrome.

* This paper was published in full in the last issue of this Journal (*Annals of the Rheumatic Diseases*, 1951, **10**, 277). Dr. Polley reported that the instrument was being manufactured without patents by V. Mueller and Co., Rochester, Minn.

Discussion.—DR. J. J. BUNIM (*New York*): I will give a brief clinical summary of two of the patients observed by us and included in Dr. Dobriner's series:

(1) The first patient developed rheumatoid arthritis in 1937, at the age of 43, 14 years before the steroid studies were begun. The proximal interphalangeal and metacarpophalangeal joints, wrists, and elbows were symmetrically involved, and the left ankle was severely affected. Huge subcutaneous nodules were present over the metacarpophalangeal joints of both hands and the free borders of both ulnae near the elbow. At the time of Dr. Dobriner's studies, the sedimentation rate was 70 mm., and both the haemolytic streptococcus and sheep-cell agglutination tests were positive.

(2) The second patient developed psoriasis at the age of 43 and rheumatoid arthritis 1½ years later. The onset of arthritis occurred 14 months before determination of the urinary steroids was done by Dr. Dobriner. The interphalangeal joints of the right thumb, right great toe, metatarsophalangeal joints of several toes of both feet, left wrist, and right ankle were involved. In addition, the distal interphalangeal joint of the right ring finger was swollen, red, painful, and tender. It is noteworthy that none of the proximal interphalangeal joints were affected. No subcutaneous nodules were present. Extensive psoriatic lesions were present over the back, buttocks, and posterior thighs. The erythrocyte sedimentation rate was 55 mm. per hour (Westergren). The haemolytic streptococcus and sensitized sheep-cell agglutination tests were negative.

DR. HOWARD F. POLLEY (*Rochester, Minn.*): A patient from the Mayo Clinic included in Dr. Dobriner's report was a man, aged 22, who had had rheumatoid arthritis and rheumatoid spondylitis for about 3 years. Motion in the neck, shoulders, spinal column, and knees was considerably limited. He could abduct the right arm only 65 degrees. The knees were slightly swollen. It was hard for him to put on his socks and shoes. Difficulty in combing his hair was solved by wearing a crew cut. Roentgenogram revealed bilateral sacro-iliac arthritis. The sedimentation rates were elevated. Cortisone given intramuscularly in doses of 100 mg. daily for 32 days had a marked antirheumatic effect; this began to disappear 9 days after administration of cortisone was stopped, but the patient maintained about one-half the relief for nearly 3 months.

Dr. Dobriner has given us some interesting, important and fundamental data.

DR. IAN F. SOMMERVILLE (*Edinburgh, Gt. Britain*): Dr. Dobriner's paper was of especial interest to me in the light of certain studies in steroid metabolism previously carried out by Dr. G. F. Marrian and myself in the University of Edinburgh. These studies were directed towards the problem stressed by the speaker—whether there is a relative or an absolute deficiency of adrenocortical secretion in rheumatoid arthritis. We studied the proportion of administered progesterone excreted as urinary pregnanediol as a model reaction in normal and arthritic human subjects, and we showed that an abnormally high proportion of the metabolite is excreted by the arthritic group. Progesterone was chosen because of the well-established status of its metabolite, and because there are theoretical grounds for the belief that this hormone and the adrenocortical hormones may follow at least one common metabolic pathway—the formation of pregnane derivatives and reduction of one or more ketonic groups.

This observation emphasizes the importance of extending such a study to the intermediary metabolism of cortisone itself, both in the human subject and at the cellular level, and is at least indirect evidence of an abnormal metabolism of adrenocortical hormone in rheumatoid arthritis.

Further work is in progress to establish the incidence of the abnormality of progesterone metabolism in other diseases. Preliminary observations indicate that it is not present in diseases sharing certain clinical features with the rheumatic group—for example tuberculosis, and osteoarthritis. Other diseases which respond to cortisone or ACTH have yet to be studied. As more cases are screened, we find that some arthritics fall within, or only slightly above, normal limits, and it will be interesting to correlate the degree of steroid metabolic defect with some clinical feature of the disease.

If the abnormality is indeed fundamental, then it would be expected to persist despite the administration of ACTH or cortisone. Preliminary studies with ACTH indicate that this is so.

In conclusion, I would suggest that an elucidation of the biochemical nature of this defective handling of administered steroid may lead to a significant contribution, not only to the treatment of rheumatoid arthritis, but to an understanding of the role of the steroid hormones in pathogenesis.

DR. J. J. R. DUTHIE (*Edinburgh, Gt. Britain*): I have been associated with the work described by Dr. Sommerville, which suggests an abnormality in cases of rheumatoid arthritis in the metabolism of steroids by the tissues. The evidence put forward by Dr. Dobriner would suggest that there is also some abnormality in the adrenal gland itself. Both conditions may be present, but the fact that the abnormal steroid metabolites disappear from the urine when ACTH and cortisone are

administered is rather puzzling. That they should disappear with cortisone is understandable, but I should have expected them to increase on the administration of ACTH if the urinary metabolites are derived from an abnormal steroid produced by the adrenal. The fact that they disappear suggests the possibility that the primary defect may lie in the pituitary, which may be secreting an abnormal form of ACTH and that adrenal function reverts to normal when ACTH is given by injection. I should certainly like to hear Dr. Dobriner's views on this point.

Observations on Local Action of Adrenocortical Steroids. By BURTON L. BAKER, *Ann Arbor, Mich.* (by invitation).

In contrast to numerous other types of hormones, it is possible to demonstrate a localized action by adrenocortical hormones, particularly those of the C-11 oxygenated group. This spatial limitation of effect appears to be made possible by a rapid peripheral utilization of the adrenal hormones, so that, at low doses, the amount absorbed into the blood stream is insufficient to exert a systemic effect. In addition to other structures, fibro-elastic connective tissue is modified by the local action of adrenocortical steroids with all its major components involved, including cells, fibres, and ground substance. Prolonged direct application to the skin of adrenal extract causes thinning of the dermis with involution of fibroblasts, a temporary retardation in the formation of granulation tissue, and acceleration in the spreading action of hyaluronidase. These modifications are limited, for the most part, to the area of application. However, they cannot be maintained indefinitely because ultimately the skin returns to normal in spite of continuation of the treatment. Thus, a local loss in responsivity to the action of the adrenal hormones is demonstrated. When compared on the basis of their capacity to inhibit growth of hair by local action, the C-11 oxygenated steroids are more potent than the C-11 non-oxygenated steroids. Nevertheless, 11-desoxycorticosterone in large doses will inhibit the growth of hair and accelerate the spreading action of hyaluronidase. Many of the connective tissue responses to adrenocortical steroids are illustrated in striking fashion in the tissues immediately surrounding implanted pellets of pure adrenal steroids. Alterations in fibroblasts seem to be of primary significance in accounting for the other effects of adrenal hormones on connective tissue.

Discussion.—DR. CHARLES RAGAN (*New York*): I wish to compliment Dr. Baker on his paper, which is a superb piece of work.

Our main concern has been with the response of tissue to trauma as modified by the parenteral administration of cortisone, and our results corroborate those of Dr. Baker. Certainly, we can confirm everything he has said concerning the response of traumatized tissue.

However, I think that the interpretation of these results is still open to some speculation, and we, as clinicians, have found ourselves in the middle of a controversy of anatomists concerning the origin of the fibroblast, about which there are two schools of thought. The one which is most attractive, which would fit into this hypothesis, is that championed by Bloom and his school, who feel that at least one of the precursors of the fibroblasts is the macrophage. It has been shown by Dougherty and Spain that, during hyperadrenalism in animals and in humans, there is a decrease in the number of wandering cells and macrophages in an area of trauma.

Lurie and Gordon have shown that *in situ* the macrophage is phagocytic, Lurie in liver and Gordon in spleen. We have done this with local traumatized areas and find that *in vivo* the macrophage is phagocytic but does not wander into an area. The next phase in the inflammatory process has been studied by Duthie (*Edinburgh*), and by Bethel (*Ann Arbor*), who have found there is a decrease in capillary permeability after the administration of ACTH or cortisone.

The next phase in the modification of the inflammatory process has been studied by Ebert, Michaels, and Wood who have found that there is a decrease in margination of leucocytes in capillaries round an area of trauma, during hyperadrenalism.

Which is the first site to be modified in this modification of the inflammatory reaction? We are not prepared to say whether one must start with the inability of the leucocytes to marginate through either the decreased capillary permeability or a decrease in the number of invading macrophages or in fibroblast proliferation.

We can confirm Dr. Baker's work, as far as the local action of cortisone is concerned, in work

done by Howes. Ear wounds were made and cortisone ointment applied to one ear and plain ointment to the other. There was a marked decrease in the granulations appearing in the cortisone-treated ear.

Concerning the escape phenomenon, whereby this is not a complete inhibition but solely a delay, we have evidence to show that this also is a local effect, since, if a wound be made in an animal made hyperadrenal with cortisone, it will heal in 14 days, but will show marked inhibition of repair after only 5 days.

I should like to ask Dr. Baker a question. Since he has demonstrated a local effect of ACE and cortisone on non-traumatized connective tissue, does he presuppose that this tissue has some turnover ? In other words, do the fibroblasts disappear or is there a failure to replace them ?

DR. P. OPSAHL (*New Haven, Conn.*): I should like to ask Dr. Baker about the primary action on the enzyme, and whether he used adrenal extract *per se* or cortisone in the control.

DR. BAKER: I am pleased to have both Dr. Ragan and Dr. Opsahl participate in this discussion, because their work has greatly stimulated us throughout our investigations.

First, a few words about the origin of fibroblasts. Dr. Ragan's comment concerning the possible conversion of macrophages into fibroblasts in the formation of granulation tissue is of extreme interest and merits investigation with respect to the action of adrenocortical hormones. However, it seems to be the opinion of most anatomists, that the majority of the fibroblasts of granulation tissue arise by proliferation of pre-existing cells of a similar or more primitive type.

With respect to the enquiry concerning the turnover of fibroblasts under these experimental circumstances, there is little that can be said. Without the employment of a technique whereby cells are tagged, I do not see how the question can be answered. Most of the results described could be explained on the basis of damage to cells which are already present due to the development of a local state of hyper-adrenocorticalism. Whether there exists a problem of turnover of cells I do not know.

As for Dr. Opsahl's question whether the primary action is on the enzyme or the cell, I should like to reiterate our contention that probably many of the changes induced in fibro-elastic connective tissue by the local action of adrenocortical steroids are due to suppression in metabolism of the fibroblast. If this is so, intra-cellular enzyme systems must be affected.

The extract used in these studies was prepared by the Upjohn Company, and is a hog adrenal extract dissolved in 25 per cent. alcohol. In all of these studies the solvent 25 per cent. alcohol was used as control.

Adrenal Cortex in Rheumatic Diseases, with Special Reference to the Effects of Cortisone and ACTH. By LEON SOKOLOFF, JOHN T. SHARP, and EDWIN H. KAUFMAN, *New York* (by invitation).

In a systematic study, it is demonstrated that the adrenal cortex in rheumatic diseases show no changes that distinguish it from the adrenal cortex in non-rheumatic diseases. Three types of measurements have been made:

(1) weight
(2) cholesterol content
(3) a quantitative analysis of the zonal architecture

Control values were obtained on healthy individuals dying of trauma and of disease states of many types. Small doses (2,000 mg. or less) of ACTH or cortisone do not cause appreciable changes. Large doses of ACTH may induce marked hypertrophy that apparently regresses after cessation of therapy. Large doses of cortisone sometimes result in atrophy. The cortex may be restored to normal size when the medication is discontinued. In rheumatic diseases the adrenal responds morphologically to ACTH and cortisone in the same way as it does in non-rheumatic diseases. Permanent morphological alteration does not result from the use of these compounds.

Discussion.—DR. M. PATTERSON (*New York*): Parallel with our clinical observations of the effect of prolonged use of cortisone acetate in patients with rheumatoid arthritis, animal studies were conducted to determine whether daily injections of cortisone produced irreversible changes in the adrenal glands.

Fifty adult white rats, divided equally as to sex, were given intramuscular injections of cortisone acetate 3 mg. daily for 11 days. This dose was ten times the equivalent of a human dose of 100

mg./day and the 11-day injection period in the rat was equivalent to 1 year of life in man. Sixty-six rats provided suitable control material. The cortisone-treated rats were divided into five groups. Group 1 was killed at the end of the injection period to determine the probable maximal cortisone effect. The other four groups were killed at various periods after the last injection, corresponding to 4, 6, 15, and 33 months in man, and the effect of cortisone was determined by adrenal-gland weight and by histologic study of the adrenals stained by haematoxylin-eosin and Sudan IV.

Histologically the effect of cortisone upon the adrenal gland consisted of a narrowing of the cortex and a decrease in the sudanophilic material in the cytoplasm of cells of the fasiculata and reticular zones. These were not identical in the sexes. In the male rats the effect of cortisone reached a maximum at the 6-month period and then improved, so that at 15 and at 33 months the effect was absent. In the female rats the cortisone effect present at the 1- and 4-month periods was less pronounced than in the males; at the 6-month period the females showed a slight decrease in sudanophilic material, whereas the males at this period had shown the most marked effect; at 15 and 33 months the female adrenals appeared normal.

On the basis of adrenal weight, the female rat adrenal had completely recovered after a period corresponding to 6 months in man, whereas the male adrenal was not completely normal at this period. Both sexes showed complete recovery at 15 months. The adrenal of the treated male rat always showed a greater decrease in weight as well as greater reduction in the sudanophilic substance than did the adrenal of the female rat.

These studies showed that the adrenal glands of the adult white rats injected daily with cortisone in doses ten times the equivalent of the human dose of 100 mg. a day, for a period corresponding to one year in man, completely recovered from the changes effected by the steroid. No permanent damage was found, and recovery from the cortisone effect was more rapid in the female.

DR. E. P. ENGLEMAN (*San Francisco, Calif.*): I only wish to state that in patients whom we have had on cortisone therapy for as long as 14 months continuously, we have demonstrated an excellent eosinopenic response to ACTH administered intravenously, despite the simultaneous oral administration of cortisone. This was usually demonstrated in a period of 1 to 2 days.

DR. SOKOLOFF: The observations of Dr. Patterson largely confirm ours. I suggest that cortisone, even in one large dose, is apparently without destructive effect upon the adrenal.

Changes in Sternal Bone Marrow and Peripheral Blood during Cortisone Therapy in Rheumatoid Disease. By LESTER M. GOLDMAN and HERMAN H. TILLIS, *Newark, N.J.*

Sternal marrow and peripheral blood studies were made in 22 cases of rheumatoid disease receiving cortisone for a continuous period of 15 to 37 days. Marrow studies revealed a significant shift to maturity in granulocytes and a marked increase in the number of lymphocytes at the end of the period of observation. The changes seen in various leucocyte levels in the peripheral blood during the period of observation were discussed. It was suggested that an anti-inflammatory action of cortisone may explain an initial lymphopenia and subsequent lymphocytosis.

Discussion.—DR. J. J. BUNIM (*New York*): The importance of the observation reported by Dr. Tillis and Dr. Goldman depends on the significance of the changes observed. It is also important to bear in mind that the difference in the number of cells is relative not absolute. Was the shift observed after cortisone administration associated with an increase in the total cellularity of the bone marrow, and if so, how did it affect the myeloid-erythroid ratio and the lymphocyte-erythroid ratio ? If, for example, there were an increase in cellularity, and if, furthermore, the erythroid elements remained constant, then an increase in the lymphocytes and/or the mature granulocytes would account for a resulting fall in the relative percentage of immature granulocytes. In such circumstances, it would not be valid to conclude that cortisone inhibited the normal reaction to inflammation. That cortisone administration is followed by a recession of the inflammatory reaction in tissues such as the synovialis, the subcutaneous nodules of rheumatic fever, and the corium in certain rheumatic diseases, has been demonstrated repeatedly. It has also been shown by Wood that at the site of bacterially-induced inflammation, cortisone depresses the process of cellular exudation. The lesions consequently contain relatively acellular oedema-fluid in which many more bacteria are present than in the lesions from control animals. Exactly such histopathological circumstances were observed in one of our patients who died of an overwhelming pneumococcal pneumonia while under ACTH therapy.

To attribute to cortisone the capacity to inhibit in the bone marrow a natural granulocytic response to inflammation, may lead one erroneously to shift the emphasis from the local inflammatory lesion to a haematopoietic structure, as the important site of cortisone action. The results reported by Dr. Tillis and Dr. Goldman are at variance with those published last year by Rosenthal, Yager, and Litwins of New York. The differential counts in the bone marrow of a series of patients with rheumatoid arthritis treated with cortisone by these workers showed no significant change. For example, before and after cortisone, the myelocyte count was 22 and 24 per cent., the non-segmented neutrophil count was 30 per cent., the segmented neutrophils were 14 and 13 per cent., and the eosinophil count was 3 per cent. More recently, Sussman and Antopol conducted similar studies in cortisone-treated mice and again found no " inhibitory effect of cortisone on cell proliferation in the bone marrow ".

We should like to ask Dr. Tillis whether the fall in the immature granulocytes may not have been secondary to a relative increase in the lymphocytes or mature granulocytes. Is it not possible that the lymphocytosis in the bone marrow was secondary to the lymphopenia in the peripheral blood ? Would not the hypothetical anti-inflammatory effect of cortisone imply an inability of the bone marrow to respond adequately to an intercurrent infection ?

DR. C. L. STEINBERG (*Rochester, N.Y.*): What interested me was not so much the lymphocyte response that Dr. Tillis emphasized, but the change in the plasma cells. If you recall, he reported that the plasmacytes increased to an average of 0·6 from 0·3 per cent.; and if one recalls that the plasmacytes are markedly increased in the bone marrow in the disease multiple myeloma, and that in the same disease the gamma globulin is markedly elevated, and if one keeps in mind that gamma globulin is intimately associated with the immune response, then certain conclusions may be drawn.

Gamma globulin is increased in disseminated lupus erythematosus, which is the opposite of what one would expect. The total globulin is usually elevated, and when the response to either ACTH or cortisone is obtained, the total globulin drops. Other observers have seen the same thing to occur in rheumatoid arthritis.

It seems to me that one of the reasons for the discrepancy given this morning is the fact that 500 cells are insufficient to count, since at least 5,000 cells are required in order to be reasonably accurate as to the haematological picture that is present in the bone marrow.

Lastly, I wish to bring up a controversial point. Are the lymphocytes produced in the bone marrow ? The bone marrow has been diluted with peripheral blood by this method, and we are not getting a true picture of what is occurring in the bone marrow.

DR. ABRAHAM S. GORDON (*Brooklyn, N.Y.*): I want to ask Dr. Tillis what method he used in the study of the contents of the bone marrow. I think the entire picture of the changes noted depends upon the *method* used in the study of the cellular content of bone marrow, but that is not described. Can he give us any details on this matter ? How did he dispose of the intercellular substance, or the walls of the sinuses of the marrow, and how did he dispose of the fat in the marrow ?

I call attention to this because about fourteen years ago I described a special method of studying cellular contents of marrow and went into great detail to eliminate all the extraneous material so as to be able to show exactly the differential elements in the different types of the cells in the marrow. I therefore think the method used is extremely important.

Often unidentified cells or very early primordial cells are mistaken for lymphocytes. The results may vary, depending upon the technique. I have seen some of these data on the screen and they are completely at variance with some of my findings when studying the marrow.

DR. TILLIS: As regards the erythroid elements, we felt we could arrive at no conclusions. It must be realized how this study was started. It was done in a routine examination early in 1950, when we were trying to evaluate patients who had taken cortisone; at that time we did not know what the effect of cortisone on the bone marrow was going to be, any more than we knew what its effect was going to be on the spinal fluid which we studied. We felt that because of the transfusions and the haematinics we could arrive at no conclusions regarding erythroid elements, and therefore made no effort to do so.

Regarding eosinophil studies on mice, the dosage that was used over a period of 17 days was so tremendous that I feel that no observer can compare them with the human from that standpoint.

Regarding the technique of bone marrow aspirations, Dr. Goldman performed these in the manner that is usual in our hospital.

Our findings showed an increase of the lymphocytes in the bone marrow after cortisone therapy.

Aortitis and Aortic Endocarditis, an Unrecognized Manifestation of Rheumatoid Arthritis.

By WALTER BAUER, WILLIAM S. CLARK, and J. PETER KULKA, *Boston, Mass.*

The onset of pericarditis and subsequently aortic regurgitation during an exacerbation of rheumatoid arthritis, first observed some years ago, called our attention to the possibility that carditis may be a manifestation of rheumatoid arthritis. Additional evidence favouring this postulate had been noted previously; namely, that our rheumatoid arthritic patients with valvular heart disease had a higher incidence of lone aortic regurgitation than did a comparable group of patients with rheumatic heart disease.

Since then we have accumulated sufficient data to permit us to conclude that aortitis and aortic endocarditis do occur as a manifestation of rheumatoid arthritis. The clinical and pathological features of this type of heart disease are sufficiently distinctive to exclude syphilis and rheumatic fever as aetiological agents.

Discussion.—DR. THEODORE B. BAYLES (*Boston, Mass.*): We have all been interested in this report on the presence of heart disease associated with rheumatoid arthritis. The figures given concur closely with what we reported 8 years ago, and it is obvious that the inflammatory reaction in connective tissue in rheumatoid arthritis can occur in and about the heart as it does in other parts of the body. We did not observe this significant aortic lesion reported this morning.

DR. EDWARD F. ROSENBERG (*Chicago, Ill.*): Among the cases studied some years ago by Dr. Baggenstoss, Dr. Hench, and me, were two instances in which the heart showed nodular lesions similar to those described this morning by Dr. Bauer. We considered these distinctive in appearance from other inflammatory lesions observed in the hearts of this group and we compared them to subcutaneous nodules of rheumatoid arthritis. We considered these a special cardiac lesion of rheumatoid arthritis. I agree with Dr. Bauer that serious heart disease is commonly present in rheumatoid arthritis patients, and that is for some reason rarely detected by our present clinical examinations.

The question whether rheumatic fever is related to rheumatoid arthritis, is still an open one in my mind. In a majority of the cases, pathological lesions encountered in the hearts of persons dying with rheumatoid arthritis cannot be distinguished by capable pathologists from the classic lesions of rheumatic fever.

DR. GRANVILLE A. BENNETT (*Chicago, Ill.*): For the purpose of this meeting, I should like to record one other instance of an aortic lesion in association with rheumatoid arthritis. This was in a young boy who developed progressive rheumatoid arthritis at something less than 3 years of age. The arthritis progressed rapidly and extensively, so that at the time of his death, at the age of 8, he was crippled and deformed, and had also contracted a panophthalmitis which resulted in blindness in one eye.

At autopsy it was found that he had a marked aortitis with early aneurysm formation. On histologic examination the aortic valve showed thickened cusps, and the proximal portion of the aorta for a distance of about 3 cm. showed changes practically identical with those described by Dr. Bauer. This lesion, as he pointed out, is exceedingly difficult, if not impossible, to distinguish morphologically from an active syphilitic aortitis. However, in this case, as in Dr. Bauer's cases, there was no evidence of syphilis. Careful serological studies gave negative results and there was no historical evidence of syphilis.

I think that in both these cases we are dealing with instances of rheumatoid arthritis in which the connective tissue structures of the aorta have been selectively involved. There were no lesions in our patient to suggest rheumatic fever.

In another case there were signs of polyserositis and periarthritis in association with rheumatoid arthritis, but in this instance there was a marked overlap between the various types of connective tissue disease and rheumatoid arthritis.

DR. WALLACE GRAHAM (*Toronto, Canada*): I should like to ask Dr. Bauer whether he has observed these lesions in any patient suffering from pure rheumatoid arthritis. Unless I am mistaken, all the cases presented have had spondylitis. To those of us who still feel that there are good reasons for separating rheumatoid arthritis from ankylosing spondylitis, these aortic lesions occurring only with spondylitis would appear to furnish additional evidence of a clear-cut difference between the two conditions.

DR. CHARLES W. WAINWRIGHT (*Baltimore, Md*): Were there lesions in other tissues which might simulate lupus erythematosus ?

A MEMBER: Has Dr. Bauer employed histamines ?

DR. J. J. R. DUTHIE (*Edinburgh, Scotland*): It seems to me significant that in all the cases described by Dr. Bauer the spine was involved. In Britain we still tend to the opinion that rheumatoid arthritis and ankylosing spondylitis are different diseases, although we are well aware that similar changes in the peripheral joints may occur in both.

DR. CHARLES RAGAN (*New York*): I should like to know whether these patients with spondylitis had typical rheumatoid nodules.

A MEMBER: I should like to ask Dr. Bauer whether these were uniform findings in all the various parts of the heart and whether they were examined in different sections.

I should also like to ask him if any Aschoff bodies were present in any of the hearts that he examined, and to the question that has just been asked, whether the same lesions were not found in other parts of the vascular system or in other parts of the body.

DR. BAUER: I called attention to the fact that although all patients had spondylitis, approximately 75 per cent. of them also had peripheral joint disease. To date, we have not seen this type of valvular heart disease in patients with only peripheral joint involvement. In two cases the peripheral joint disease was so marked that the minimal spondylitis might have been overlooked. In some of these patients the disease began in the peripheral joints, and evidence of spondylitis was not seen until some years later. Cases of this type indicate the need for determining the incidence of spondylitis in rheumatoid arthritis of the peripheral type. This can only be established by obtaining routine *X* rays of the spine in a large number of such cases.

Our group has always considered spondylitis as a form of rheumatoid arthritis and not as a distinct disease entity. We admit that the absence of nodules and the predominance of males in patients with spondylitis favour the latter point of view. However, much about rheumatoid arthritis remains unknown, and until these gaps in our knowledge are filled, we cannot explain exceptions or establish additional disease entities.

Regarding lupus erythematosus, the answer is No.

We have treated two such cases with ACTH without favourable effect on the heart disease.

One of the patients with pericardial nodules had approximately one hundred subcutaneous nodules, but no nodules were found in the myocardium of the cases here reported, though they have been observed by Rosenberg and others.

Chemical and Histological Studies of the Fibrinoid Material of the Subcutaneous Rheumatoid Nodule. By THOMAS KANTOR, LEON SOKOLOFF, ALFRED SMITH, and MORRIS ZIFF, *New York* (introduced by Dr. Currier McEwen).

The concept of collagen disease requires a detailed consideration of the composition of fibrinoid since the fibrinoid change is the anatomical common denominator of conditions grouped under this concept. Methods have been devised in this laboratory for the separation of fibrinoid from the remaining connective tissue structures of the subcutaneous rheumatoid nodule. Using 1 to 2 mm. slices or minces of this tissue, it has been found that the fibrinoid regularly present is readily separated by treatment with 0·1 N NaOH or crystalline trypsin solutions. Serial sections have been made of the material remaining after 24-hour extraction. With conventional staining techniques known to characterize fibrinoid, it is estimated that at least 80 per cent. of the fibrinoid material has been removed by these methods. In contrast, borate buffer solutions at *p*H 7·8, streptokinase-activated plasmin, and testicular hyaluronidase solutions remove only very small amounts of fibrinoid. The separated extracts have been analysed for hydroxyproline by the radio-iodine isotope derivative method of Keston and others, which is sensitive to 0·1 gamma hydroxyproline. In analyses of two nodules by this technique, only trace amounts of hydroxyproline were found in the extracted fibrinoid. This suggests that the fibrinoid of the subcutaneous rheumatoid nodule is non-collagenous in origin. In support of this point of view, it has been observed that fibrinoid material in sections of the subcutaneous rheumatoid nodule is not digested by a very active clostridial collagenase.

Discussion.—DR. J. P. KULKA (*Boston, Mass.*): I want to compliment Dr. Kantor and his associates for showing so elegantly that fibrinoid is not of collagenous origin.

One point that Dr. Kantor made indirectly I should like to emphasize, namely, the distinction

between fibrinoid, a morphologically distinct substance, and fibrinoid degeneration, a term which, as originally used, combines

(*i*) the presence of fibrinoid,
(*ii*) the connective tissue changes which are frequently associated with fibrinoid,
(*iii*) the hypothesis that fibrinoid is derived from a chemical change in the intercellular substances.

This combination in a single term of three different meanings has, I think, caused considerable confusion in the literature.

Dr. Kantor talked about fibrinoid, the morphologically distinct substance. He has demonstrated a type of approach by which we may be able to determine the chemical nature of this substance. The next step will be to determine the nature of the relationship between fibrinoid and the degenerative changes in the connective tissue, which are the most obviously damaging features of the rheumatic lesions.

DR. GRANVILLE A. BENNETT (*Chicago, Ill.*): Some years ago, when being pushed to state what fibrinoid is, I could think of nothing better to say than that it represents something added to connective tissue, perhaps only plasma soaking of connective tissue. I feel that the present study lends support to the concept some of us have had that fibrinoid is not strictly a change in the composition of collagen.

I think that fibrinoid change—and I prefer to speak of it as fibrinoid change rather than fibrinoid degeneration since we do not know just what the alteration is—is seen in various stages of development. The lesions that were demonstrated so beautifully this morning, are possibly late lesions. If we were to look at some of the earlier lesions we might find material that stains histochemically in the characteristic fashion of fibrinoid, but we might see connective tissue fibrils extending completely across the lesion at the same time.

In what we consider to be older lesions, complete breakdown of all the connective tissue substances occurs in the centre of the nodules. In fact, some lesions become cystic and may contain only yellowish, amorphous, glandular or curdlike material in their centres.

Thus the degree of change or the amount of disintegration of connective tissue depends, I believe, upon the duration of the lesion. The older nodules show the most complete breakdown.

I hope you will comment on your findings in light of the stages of development of the nodules.

DR. CURRIER MCEWEN (*New York*): I can add only the comment that most people have been somewhat dissatisfied with the term " collagen diseases " and that this is perhaps one more reason to be dissatisfied with it.

DR. HUGO A. FREUND (*Detroit, Mich.*): I am glad that the distinction was made between the formation of fibrinoid and fibrinoid degeneration. Fibrinoid is formed in so many different conditions. We have been particularly interested in fibrinoid in our pathological laboratories, because we know that fibrinoid is found in many allergic manifestations, in the Aschoff body, in lymphocytic accumulations, and, as discussed to-day, in subcutaneous nodules. Altshuler and Angevine (1949) suggested the possibility of fibrinoid formation coming originally from the acid mucopolysaccharides. In that connection, we have studied, and recently reported, that in rheumatoid arthritis an excessive formation of mucoproteins and mucopolysaccharides occurs. Methods of measuring the mucoprotein have been devised, though we are not yet certain about their accuracy.

I should like to offer the suggestion that mucoproteins and mucopolysaccharides are the precursors of fibrinoid which in time undergoes degeneration, and that the entire process is initiated by a hormonal defect or by a failure of a specific enzyme formation.

DR. KANTOR: First of all, Dr. Freund mentioned the role of the intercellular ground substance in the production of fibrinoid and referred to Altshuler and Angevine (1949). We certainly confirm the findings of Altshuler and Angevine; all sources of fibrinoid that we have examined are positive with the periodic acid-leuco fuchsin stain after appropriate controls to eliminate glycogen and lipids. Most investigators believe this indicates the presence of an acid mucopolysaccharide. We are now trying to design a way of treating our nodule minces in order to determine the acid mucopolysaccharide content of the fibrinoid. This will probably be a difficult job since, by our methods, we almost certainly remove the ordinary tissue mucopolysaccharides as well as the fibrinoid. In any case, this will only resolve the question of concentration; it neglects what may be more important—namely, the physical and chemical state of these substances.

Dr. Bennett points out, quite correctly, that our tissues represent late lesions. They are all

Altshuler, C. H., and Angevine, D. M. (1949). *Amer. J. Path.*, **25**, 1061.

from nodules that have been present from 1 to 3 years. However, we were quite definite in picking solid, and therefore, presumably younger, portions of the nodules for analysis. In fact, only one of the nodules had cystic change in one portion.

Dr. Bennett's point about the earlier lesions looking as though they were " painted " with fibrinoid material is a good one. We think that is probably what the process represents. Once one takes the fibrinoid material out, normal collagen is apparently left underneath. It is as though fibrinoid material were absorbed on to the collagen fibres.

We did have one early lesion which had been present for a week or 10 days, but to our dismay, we lost it because of technical difficulties.

Dr. McEwen pointed out that the concept of collagen disease is perhaps seriously affected by this work. Klemperer (1950, 1951) has pointed out the inherent dangers in this concept. His concept of collagen disease has little to do with the protein collagen itself. He originally meant, in the older pathological sense, to include an equal consideration of all of the intercellular elements of the connective tissue. Thus, he includes in this concept the ground substance elements and elastin as well as the collagen fibre.

Comparative Effects of Compound F (17-Hydroxycorticosterone) and Cortisone injected locally into the Rheumatoid Arthritic Joint. By JOSEPH L. HOLLANDER, ERNEST M. BROWN, Jr., RALPH A. JESSAR, and CHARLES Y. BROWN, *Philadelphia, Pa.*

Injection of 25 to 50 mg. cortisone directly into the synovial cavity of one inflamed knee joint in each of eleven patients with rheumatoid arthritis caused no local beneficial effects as measured by symptoms and physical signs, by lowering the cell count of the synovial fluid, or particularly by a significant reduction (i.e. more than 0·4° C.) in intra-articular temperature. In contrast, the administration of 25 mg. Compound F (Kendall) into a single diseased joint in each of nine patients with rheumatoid arthritis resulted in marked local improvement in symptoms and signs, a fall in the cell count of the synovial fluid, and a significant fall (0·6° to 1·9° C.) in intra-articular temperature within 24 hrs. Contralateral diseased joints used as controls showed no significant change, nor were there other signs of systemic effect.

In two patients a measurable benefit was noted with doses of 10 to 15 mg. Compound F, but most required 25 mg. The joint temperature returned to pre-treatment level within 48 hrs in most instances. Some clinical improvement persisted as long as 10 days after a single injection of 25 mg. Compound F into the joint. It would appear that the demonstration of a direct action and beneficial effect of Compound F, in apparent contradistinction to Compound E, upon the tissues of the rheumatoid arthritic joint, further emphasizes the physiological importance of Compound F.

Discussion.—DR. CARL STEVENSON (*New York*): We have had experience with the intra-articular injection of Compound F acetate in fourteen patients with rheumatoid arthritis; one had injections into the hip joint, and the others into the knee joints. The initial dose was always 25 mg., with subsequent doses of 25 or 50 mg. Injections were made at intervals of from 3 to 42 days. The short intervals occurred during the early part of this study when an attempt was made to suppress all signs of inflammation in the treated joint. In this group of patients, twelve of the fourteen reported more than 50 per cent. relief from pain and stiffness; six patients reported *complete* relief of symptoms when injections were made weekly.

The degree of symptomatic improvement did not always parallel the objective changes. In most instances the patient reported relief from pain and stiffness before there was a significant change in the physical signs. There was, however, a moderate to complete improvement in the injected joints of eleven of the fourteen patients. During the interval between injections objective worsening appeared 2 to 14 days before symptomatic worsening.

These preliminary studies suggest the following generalizations:

(1) Compound F can be given safely into the joint cavity.

(2) It has a local suppressive effect on joint inflammation as measured clinically in most patients. Evidence that the effect is local is shown by the complete absence of changes in other joints.

(3) 50 mg. Compound F acetate usually produced a greater improvement with longer duration than doses of 25 mg.

Klemperer, P. (1950). *Ibid.*, **26**, 505.
—— (1951). *Amer. J. Med.*, **10**, 405.

(4) Aspiration of all conveniently available fluid from the joint prior to injection of Compound F seemed to enhance beneficial effect.

(5) The average duration of improvement was between 10 and 20 days after injection; two patients showed improvement for 28 and 42 days respectively.

(6) The cell count of joint fluid showed a decrease in total cells with a return of lymphocytes in all patients.

DR. MARIAN W. ROPES (*Boston, Mass.*): Dr. Hollander's report of the temperature changes in cortisone and Compound F are clear-cut. Has he any explanation of their meaning as regards the physiology of the joint.

We have not tried Compound F, but have given cortisone by intra-articular injection to three patients. All had some subjective and objective improvement, but we found that the cell count in the synovial fluid was usually the same or slightly elevated. The polymorphonuclears fell in one case, and viscosity rose in all cases, to the same degree as one would expect from intramuscular or oral cortisone.

There were two unusual findings: in one patient with bilateral knee effusions, radio-active sodium entered more rapidly into the treated joint than into the opposite joint, which perhaps indicates increased inflammation in the joint into which cortisone was injected. In another patient the electrophoretic pattern of fluid showed a remarkable change; the gamma globulin fraction rose from 20 to 25 per cent. and the albumin dropped from 39 to 34 per cent.

DR. DAVID H. KLING (*Los Angeles, Calif.*): I have given intra-articular injections of cortisone in a large number of cases; the doses varied from 50 to 100 mg. repeated after 48 to 72 hours. Various degrees of clinical improvement were found in the majority. Re-aspiration showed a diminution of inflammation: increase in viscosity, and decrease of total cell counts and polynuclear leucocytes. However, the effects were of no longer duration than after intramuscular injections, which was disappointing as we had hoped that a depot of cortisone in the joint cavity would be only slowly absorbed and would thus have a prolonged effect. Re-aspiration, 48 hours after injection showed that the effusion contained a sediment of granular and crystalline material derived from the injected cortisone. Samples of this sediment were submitted for analysis to the Merck Laboratory, and Dr. Gibson informed me that they were unable to identify cortisone in the material.

Disintegration of cortisone by the metabolic activity of inflamed synovial tissues may explain the failure to prolong its therapeutic effect by intra-articular injections.

However, I cannot subscribe to the idea that cortisone has only a systemic effect while Compound F exerts a powerful local action. This is contradicted not only by our own experience of the immediate beneficial effect of intra-articular injections but also by the pronounced effect of local application of cortisone in some eye conditions.

Intra-articular temperature measurements are valuable but are not the only reliable indicators of inflammatory activity in the joint cavity. Clinical aspects, such as swelling, stiffness, tenderness, local skin temperature, and analysis of joint effusions, are of equal or greater importance.

DR. J. J. BUNIM (*New York*): Injection of 50 mg. cortisone acetate into the knee joints of twelve patients with rheumatoid arthritis resulted in eight in marked to moderate improvement locally. The pain, swelling, stiffness, and effusion diminished or disappeared. In the remaining four patients, there was no improvement. When cortisone was introduced into the knee several weeks after the patient had been receiving cortisone by mouth or intra-muscularly, local improvement in the articular symptoms was definitely augmented. Therefore, if it be reasoned (but this is all theoretical), that cortisone given systemically reaches the articular tissues as Compound F, it would then appear that, in the absence of evidence that synovial tissue in rheumatoid arthritis has the ability to reduce Compound E to Compound F, larger amounts of " E " are more effective than smaller amounts of " F ". In other words, if there is a difference in the action of these compounds, it would seem to be a quantitative one.

It has recently been demonstrated by Karnofsky of the Sloan-Kettering Institute that the differences between the biological effects of cortisone and Compound F vary in different experimental animals. Whereas, in the chick embryo, Compound F was found to be 30 times, and in the newly-hatched chick about 100 times, more active than cortisone, in new-born mice cortisone and Compound F were found to have the same degree of biological activity. Dr. Heard arrived at a similar conclusion when assaying these two hormones by several different techniques in mammalian systems.

In a patient with rheumatoid arthritis 50 mg. Compound E acetate was injected into one knee and 50 mg. Compound F acetate into the other. The synovial fluid from each joint was analysed before and after each injection and in addition to total and differential leucocytes counts, the

activity of an *amino*-peptidase enzyme in the synovial fluid which splits glycyl-glycyl-glycine was also determined (see Table). I should like to add here that, although studies on the enzyme activities of synovial fluid in our laboratory have not yet been completed, our results hitherto indicate that the concentration of *amino*-peptidase in the synovial fluid is probably related to the type and density of cellular infiltration in the synovial tissue. In general, synovial fluid from rheumatoid and tuberculous joints contain significantly greater concentrations of peptidases than fluid from patients with rheumatic fever, or gonococcic, traumatic, or osteo-arthritis.

The peptidase activity of serum was 5·9 before, and 7·8 after, cortisone administration.

It is our impression that cortisone injected intra-articularly is of definite value in properly selected cases, but further experience may prove that compound F is more effective.

TABLE

RESULTS OF INJECTIONS

		Right			Left		
	Knee						
	Hormone	Cortisone Acetate (50 mg.)			Compound F Acetate (50 mg.)		
	Time of Assessment	Before Therapy	After 14 days on Oral Cortisone	3 days after Injection into Joint	Before Therapy	After 14 days on Oral Cortisone	3 days after Injection into Joint
Improvement	Subjective	—	Slight	Moderate	—	Slight	Moderate
	Objective	—	Slight	Moderate	—	Slight	Moderate
Synovial Fluid	Total white blood cells	16,000	30,000	2,200	16,000	20,000	1,800
	Per cent. polymorphs	79	98	97	81	86	36
	Per cent. lymphocytes	21	2	3	19	14	64
	Peptidase activity*	19·6	16·1	5·1	19·6	18·1	4·0

* Expressed in per cent. glycyl-glycyl-glycine hydrolyzed per hour.

DR. B. F. MASSELL (*Boston, Mass.*): Was the vehicle used the same ?

DR. EDWARD W. BOLAND (*Los Angeles, Calif.*): For the past 2 months we have been investigating the effects of Compound F acetate given systemically by both the oral and intramuscular routes in patients with chronic rheumatoid arthritis. Our experience has been very limited, but so far Compound F acetate has not been found to be superior to cortisone in its antirheumatic activity. Our preliminary observations indicate that the amount of Compound F acetate needed for equivalent response may be greater, milligram for milligram. From the standpoint of adverse reactions, however, less psychic stimulation has been experienced than with cortisone. We have had no experience with Compound F used intra-articularly.

DR. WILLIAM D. ROBINSON (*Ann Arbor, Mich.*): Are the comparative studies for Compound E (cortisone) based on the changes occurring in 24 hrs after a single injection, or on the basis of repeated daily injections ?

DR. WILLIAM S. CLARK (*Boston, Mass.*): It is our impression, on the basis of limited experience, that Compound F, milligram for milligram, is equally as effective as Compound E, and that any differences in antirheumatic effects may be due to the factor of absorption. Have studies been made to determine relative rates of absorption from the joint of these two compounds. We stopped our study with intra-articular cortisone, because, on the basis of eosinophil counts, we did not feel we were keeping the hormone in the joint long enough to get a local effect. If Compound F is absorbed more slowly, its local effects may be due rather to having a higher concentration in the joint for a longer period, than to any qualitative differences between the two hormones.

DR. HOLLANDER: We feel that the joint temperature is only a measurement of the amount of inflammation present in that joint.

With regard to Dr. Kling's question, I am amazed at the amounts of cortisone he was able to inject without reaction. We have always noted reaction to doses of Compound E greater than 25 mg., and we have not yet tried doses of Compound F larger than 37·5 mg.

Referring to Dr. Bunim's case, which showed equal effects, with E and F, we have tried two such experiments with E in one joint and F in another, in cases already on cortisone. I think that the results of such an experiment are open to question. When you inject 50 mg. F into one knee and 50 mg. E into the other, there is no question that the addition to the systemic cortisone already used will have increased systemic effects which will certainly affect both knees.

In answer to Dr. Massell's question about the vehicles used, the two preparations used were E and F acetate, and the particle size was identical. We tried experiments using E alcohol, which is ten times more soluble than E acetate, and we tried cortisone tricarballylate solution locally, but neither was comparable to F acetate in local anti-inflammatory effect.

In response to Dr. Boland's remark about systemic Compound F being inferior to E, we, too, have observed less striking effects from F in the few cases we have treated systemically. We feel it may be necessary to give F frequently, in smaller doses, rather than in the single large doses of cortisone which we have been accustomed to use.

Concerning Dr. Robinson's comparison studies: in our experiments we have tried to cover the effects of both single and multiple injections. Most of our clinical effects were measured on the basis of one injection, observed until the patient experienced a partial relapse, followed by another one, and so on—not pyramiding the injections, but waiting until the first effect was over, as we wanted to see how long the benefit would last.

In answer to Dr. Clark: as far as I know the rate of absorption from the tissues of Compound F as compared with E, has not yet been worked out, and we have not yet determined the absorption rates from the joints.

I want to close by saying that we do not claim that Compound F used locally is a treatment for arthritis, nor that it has anything to do with the cause of arthritis, but the ameliorating effect is an interesting phenomenon and worthy of further study.

Significant Remissions in Rheumatic Diseases with High-Dosage Cortisone Therapy. By THEODORE B. BAYLES, FRANCIS L. COLPOYS, PAUL FREMONT-SMITH, BRUCE C. FERGUSON, and EMIL PAIGE, *Boston, Mass.*

After standard dosage ACTH and cortisone therapy in rheumatic diseases, 90 per cent. of 135 patients relapsed within 10 days after treatment. Nine patients on ACTH therapy experienced prolonged remissions. Accordingly, we treated twelve patients with high-dosage cortisone: seven cases of rheumatoid arthritis, one of rheumatoid spondylitis, one of juvenile rheumatoid arthritis, two of disseminated lupus erythematosus, and one of smouldering rheumatic fever with carditis. Previously the standard dosage of ACTH or cortisone had failed to produce lasting improvement in four.

500 mg. cortisone were administered intramuscularly daily for 14 to 28 days, to eleven adults; the juvenile rheumatoid arthritis patient received 300 mg. daily. Transient psychotic episodes in two patients and marked fluid retention in a third were the only serious temporary effects noted.

The first five patients treated were followed up for 74 to 88 days after therapy and all are in good clinical remission with no evidence of persisting hormonal effect.

Four patients followed for 13 to 32 days are in good clinical remission. Three patients have just concluded therapy.

The prolonged remissions are highly significant in view of previous experience. High-dosage therapy can be administered with safety and deserves further investigation.

Problems of Prolonged Cortisone Treatment for Rheumatoid Arthritis—Further Experiences. By R. H. FREYBERG, C. T. TRAEGER, M. PATTERSON, and W. SQUIRES, *New York*, and C. H. ADAMS, *Flint, Mich.*

Since our first report on prolonged cortisone treatment for rheumatoid arthritis was made in June, 1950, experience has been gained in many more patients and for longer treatment periods; in some patients there was uninterrupted treatment for 12 months or

longer. Also, experience has now been gained with the clinical course *after* prolonged hormone treatment has been discontinued.

Early and severe relapse of the disease after cessation of cortisone was the rule even after prolonged treatment and in patients with disease in short duration, no matter how the hormone was given. Entirely separate from relapse of the arthritis is the problem, in some patients, of severe and prolonged " post-cortisone withdrawal syndrome ". Therefore, the importance that the hormone be not considered routine treatment in patients with rheumatoid arthritis is emphasized and the necessity is stressed that the following *two* questions (not one), be considered before cortisone treatment is decided upon:

(1) What will happen when cortisone is administered ?
(2) What will happen when the hormone is discontinued ?

Clinical Effects of Cortisone administered orally to 100 Patients with Rheumatoid Arthritis. By EMERSON WARD, CHARLES H. SLOCUMB, HOWARD F. POLLEY, EDWARD C. KENDALL, and PHILIP S. HENCH, *Rochester, Minn.*

The effects of tablets of cortisone administered orally have been studied in about 100 cases of rheumatoid arthritis.

In all patients the antirheumatic effect was comparable to that resulting from the intramuscular administration of cortisone.

In most instances the required dose of cortisone was approximately the same for the oral as for the intramuscular preparation. Some cases required slightly more of the oral than of the intramuscular material. Occasionally oral cortisone seemed more effective.

The main difference between the effect of oral and intramuscular cortisone was the greater speed of onset and the more rapid wearing off of the antirheumatic effect in the case of oral cortisone. The daily dose of oral cortisone should be divided and spaced more or less equally throughout the 24-hr period.

Side-effects resulting from oral administration were similar qualitatively to those seen in cases treated by the intramuscular injection. The incidence of side-effects depended largely upon the factors of dosage, duration of treatment, and susceptibility of the patient. In a very few cases some gastro-intestinal irritation followed oral administration.

In many cases it was possible to maintain a good antirheumatic effect by the use of relatively small doses of oral cortisone which did not lead to the development of significant side-effects during the several months of administration.

Discussion.—DR. E. P. ENGLEMAN (*San Francisco, Calif.*): In order to evaluate their adrenocortical function, fourteen patients given cortisone for long terms were given ACTH intravenously for periods of 3 to 12 hours. In each patient so tested, adrenocortical function was manifested by excellent eosinopenic response to ACTH, despite the continued ingestion of cortisone. The data are presented in the Table.

It appears that irreversible adrenal atrophy is not a likely result of long-term treatment with cortisone when the prescribed maintenance doses are used. It must be noted, however, that more than one intravenous injection of ACTH was often required in order to demonstrate adrenal responsiveness. The slower than normal response to intravenous ACTH is compatible with the observation that there is a depression of adrenal cortex function during therapy with cortisone even when small doses of cortisone are used.

DR. E. F. HARTUNG (*New York*): I agree with almost every detail of what was said by Dr. Freyberg and Dr. Slocumb. My own experience extends over 17 months, in about 100 cases. In only 35 per cent. of the cases, in my experience, can we maintain a patient in reasonable comfort with a safe dose. In all the others, we are squeezed between two millstones; that is, if we give a large enough dose to keep them in reasonable comfort we produce untoward effects. Thus my results are somewhat less optimistic than those of Dr. Freyberg.

My feeling is that the safe maintenance dose is much less than 75 mg. a day. If one goes over 50 mg., in four or five divided doses, one sooner or later gets into serious difficulties.

Also, about 6 per cent. of our cases were what might be called cortisone failures, in that the effect was so ephemeral, lasting only a week or two, that it was hardly worth while to the patient, and in spite of large doses, the patient continued to be severely ill.

One last point. I still hold that gold salts occasionally produce an arrest in rheumatoid arthritis, and, in my experience, cortisone therapy militates against the beneficial effects of gold salts, even when cortisone has been temporarily discontinued, and for a long time thereafter.

TABLE
EOSINOPHIL RESPONSE TO DAILY SLOW INTRAVENOUS ACTH, 25 MG., IN RHEUMATOID ARTHRITIS PATIENTS RECEIVING CONTINUOUS CORTISONE THERAPY FOR 9 TO 14 MONTHS

Patient	Daily Dose Cortisone (mg.)	Months of Cortisone Therapy	Intravenous ACTH				
			Duration of Daily I.V. (hours)	Day of Eosinopenic Effect	Eosinophil Counts on Day of Significant Decrease		
					Pre-ACTH	Post-ACTH	Per cent. Decrease
E.B.	50	11	12	2nd	374	110	71
F.H.	37½	14	3	2nd	330	88	74
A.L.	75	14	12	2nd	220	70	69
L.L.	87½	10	3	2nd	220	82	63
W.L.	100	14	12*	4th	209	60	72
E.M.	75	11	12*	2nd	431	31	93
J.R.†	37½	9	12	2nd	572	27	95

* Duration of I.V. ACTH on previous day(s) had been 3 hours.
† Diagnosis: Chronic bronchial asthma.

DR. EDWARD W. BOLAND (*Los Angeles, Calif.*): Dr. Headley and I recently completed an analysis of our results with prolonged uninterrupted cortisone therapy in 76 patients with rheumatoid arthritis. Sixty were given cortisone continuously for periods ranging from 6 to 15 months, and 27 were treated uninterruptedly for more than one year. In the remaining sixteen patients, treatment was stopped within 6 months because of inadequate results or the development of undue hormonal complications. Our overall statistics are thus very similar to those presented to-day by Dr. Freyberg and Dr. Slocumb.

Of the entire group of 76 patients it was possible to maintain satisfactory degrees of improvement for long periods in 48, approximately two-thirds of the total.

The likelihood of promoting and sustaining satisfactory improvement depended on the initial severity of the rheumatoid arthritis more than on any other single factor. This, we think, is important, and we believe that the correlation of disease severity to results has not been sufficiently emphasized. Slightly less than 50 per cent. of severe cases were maintained under adequate control by long-term therapy, whereas the disease was satisfactorily suppressed in 70 per cent. of moderately severe cases and in 92 per cent. of moderate or mild cases. Although some severe cases failed to respond adequately even to large doses of cortisone, the chief detriment to good results was the intervention of adverse hormonal reactions. These developed at some time during the course of treatment in 40 per cent. of the patients. Whereas they were seldom of serious moment of themselves, their occurrence did influence the results. Their appearance, especially in severe cases, necessitated reduction of maintenance doses, sometimes to levels insufficient to provide desirable degrees of control of the rheumatic manifestations.

Adverse effects developed with much greater frequency when large doses of cortisone were employed. They rarely occurred with doses of 62·5 mg. a day or less, and in general their incidence was greater as larger doses of cortisone were used. The unwanted effects therefore were met most commonly during the early phase of suppressive therapy and in severe cases which required large maintenance doses.

The incidence of adverse reactions did not increase appreciably with prolongation of therapy. In our preliminary report given last year on uninterrupted administration for periods up to 4 months, the incidence was 35·7 per cent. This compares favourably with the present incidence of 40 per cent. for periods up to 15 months. We believe that this surprising similarity is due to the fact that smaller maintenance doses have been continued in most patients.

Like others, we have tried to determine the rate of adrenal functional return following prolonged therapy. Cortisone was withdrawn in eleven of our patients who had been treated uninterruptedly

for periods ranging from 8 to 14 months. During therapy there was evidence of depressed function in each case, but after withdrawal values for urinary steroids and the eosinophil response to ACTH returned to normal. The rate of recovery from these tests was variable; for the eosinopenic response to ACTH, for example, recovery occurred within 10 days at one extreme and after 90 days at the other.

DR. CURRIER MCEWEN (*New York*): These presentations represent an extremely commendable and conservative attitude, but I think that they might be interpreted too pessimistically. The hope at the beginning that these hormones might lead to cures was bound to be followed by disappointment when we found that such was not the case.

I should like to make two points. First, that we all have many patients who are tremendously better off because these hormones are available. Second, that although these hormones do not cure disease, they do accomplish more than the mere suppression of symptoms, in that they appear also to suppress the "rheumatic inflammation". I believe, therefore, that we have a right to expect that the prolonged use of cortisone over a period of years may result in a better ultimate functional status of the joints than would otherwise be the case when the disease had become inactive.

DR. RUSSELL L. CECIL (*New York*): We, too, have been disappointed in the combination of gold therapy and hormone therapy. We had the idea that by combining the two treatments, we might perhaps prolong the remission, but it has not worked out that way in the small series of twenty-odd patients that we have been following in the New York Hospital.

I have been impressed with how differently people react to cortisone; some swear by the tablets, and some think the intramuscular method is much better. The personal factor is certainly very important. Dr. McEwen made a good point, too, that we are all disappointed because cortisone has not worked quite so wonderfully as we hoped; yet we all have patients who have been greatly helped by it, and I think we should not be too pessimistic about the future.

DR. DONALD F. HILL (*Tucson, Ariz.*): We have now had a large series of patients, some on cortisone over a year, some almost two years. In spite of holding these people in remission, in a certain percentage we have noticed the progression of the disease (by *x* ray, by increased porosis of the bone, and by continued loss of cartilage), in spite of the fact that the patient remained fairly well symptomatically. In regard to the dosage, we found an extreme variation. Some required high dosages to maintain the remission but, like other workers, we have seen complications.

However, I have one patient who has required as much as 150 mg. a day. She started over a year ago on the conventional routine; we tried to reduce the dosage, but each time she would have a flare-up of symptoms; now for the last 6 months she has been out of my control, being able to buy cortisone herself, and she has insisted on taking 150 mg. a day, in spite of all the warnings. However, I have visited her to observe the effects and she still shows no bad effects or toxic symptoms.

One other feature is that so many of these patients complain of lassitude; their joints, they tell me, feel like rubber; they don't feel well; they are often depressed. You can't put your finger on anything; you examine them and find no sign of infection; the blood count, sedimentation rate, and so forth show no essential change. But very frequently I have found they have had some infection, exemplified by a low-grade fever. This is not always apparent at the clinic, but at home a noon or evening temperature is often discovered.

Some of these temperatures can be reduced by a course of antibiotics, and within a few days the patient will say he has a marvellous remission and feels much better without changing the dosage.

DR. WILLIAM S. CLARK (*Boston, Mass.*): Dr. Hill has mentioned a problem which we have been somewhat concerned with, namely the progression of the disease under the influence of cortisone, when the dosages used suppress merely the symptoms.

We have had a number of patients under long-term therapy, and in following the literal requirements of the American Rheumatism Association Criteria, we have not seen Grade I or II remissions. Although these patients are symptomatically better and even working, we have sometimes observed objective evidence of an increase in the severity of the disease. We have also seen *x*-ray evidence of progressive joint damage, and in three patients in whom we followed the synovial fluid serially, we found changes which would indicate an increase in the severity of the inflammatory process.

It disturbs us that we are making our patients feel better and making it possible for some to be up and living almost normal lives, while at the same time permitting damage to the joints which a few years ago we would have taken great pains to prevent.

I should like Dr. Freyberg and Dr. Slocumb to define what they consider satisfactory improvement, for in our opinion the improvement is nearly always mainly subjective, and to comment on the possible harmful effect of long-term cortisone therapy by masking symptoms of the disease.

DR. C. STEWART GILLMOR (*Kansas City, Mo*): We have made a study of 46 patients, some for up to 14 months. They did not respond to any treatment other than with cortisone, with which we have had very good results.

We usually give 50 or 75 mg. daily, and 100 mg. in a very few cases. Many of this group would be bedridden to-day if they had not had cortisone.

I agree with Dr. Clark that the feeling of well-being is deceptive, and we caution our patients not to exercise too much merely because they feel well.

DR. J. J. BUNIM (*New York*): At Bellevue Hospital we treated two patients during an initial attack, and one during a recurrent attack, of acute rheumatic carditis with massive doses of cortisone or ACTH after it had become apparent that they were not responding satisfactorily to usual doses. It is the impression of our group that no significant ultimate benefit was gained by large-dose administration. The resurgence of rheumatic activity following withdrawal of therapy, the total duration of illness, and the residual structural damage were not more favourably affected by massive than by ordinary doses, as is illustrated by this Table.

TABLE
USE OF LARGE DOSAGE OF ACTH IN RHEUMATIC FEVER WITH CHRONIC ACTIVE CARDITIS (8 MONTHS)

Time of Examination	Before Therapy	Course			Three Weeks after Course 3
		1	2*	3	
Hormone	None	Cortisone	ACTH	ACTH	None
Maximum daily dose	—	200	100	320	—
No. of days treated	—	27	10	28	—
Total amount (mg.)	—	2,900	835	4,960	—
Temperature	103·8°	Normal	Normal	Normal	Low grade fever
Heart rate	140	110-120	116-124	80	124
Quality heart sounds	Poor	Poor	Poor	Poor	Poor
Gallop heart sounds	Yes	Yes	Yes	Yes	Yes
Murmurs	Apical S+D	Same	Same	Same	Same
Cardiac enlargement	Moderate	Same	Same	Same	Same
Congestive heart failure	Present	None	None	None	None
C-reactive protein	Positive	Negative†	Negative†	Negative†	Positive
Erythrocyte sedimentation rate	98 mm.	9 mm.	28 mm.	19 mm.	34 mm.
Conclusions	Active carditis	Carditis persists	Carditis persists	Carditis persists	No improvement

* Interval was 14 days between Course 1 and 2, and 32 days between Course 2 and 3.
† C-reactive protein reverted to strongly positive at end of each Course.

Although the systemic effects and laboratory manifestations of the disease were all suppressed during the various courses, and to a greater degree during the periods of massive dose administrations, nevertheless the end results were not satisfactory.

DR. DAVID H. KLING (*Los Angeles, Calif.*): The introduction of oral administration has made the long-range use of cortisone more accessible to many patients, but unfortunately it has also made proper control of dosage much harder. Many patients are apt to modify the dosage either upwards or downwards, depending on the latest magazine or newspaper article they or their relatives have read; when it becomes necessary to discontinue the drug, such patients often find another doctor or pharmacist who will supply the tablets. This situation urgently requires the inclusion of cortisone among the dangerous and habit-forming drugs because addiction has occurred in addition to serious side effects.

The initial dosage should be high enough (between 200 to 300 mg. daily) to achieve the maximum improvement in the shortest time. This permits a quick evaluation of the reversibility of the process and gives the victim a glorious respite from rheumatoid arthritis. How long this vacation may be extended, how soon and how much the dosage can be reduced, depends on the circumstances, especially on the reactions, encountered in a given case.

Therefore the maintenance dosage varies from patient to patient from a few to 100 mg. or more daily and has to be adjusted from time to time.

The percentage of cases which can be maintained comfortably on low doses for prolonged periods depends on the composition of the material. If early, mild, and moderately severe cases are the most numerous the percentage will be high; it will be low if severe cases of long duration predominate.

Reduction of dosage below the level which gives definite amelioration defeats the objective of therapy. Where this becomes necessary, on account of reactions, complete suspension of the course of cortisone is the rational procedure.

Dr. Ward and his associates mentioned an increase of libido among the reactions, but this is an exception, for decrease in libido and potency during and for some time after cortisone therapy is the general rule.

DR. EDWARD F. ROSENBERG (*Chicago, Ill.*): During the past two years, I, like many other clinicians, have attempted to estimate the value of long-term administration of these hormones in rheumatoid arthritis. My attitude to-day is by no means pessimistic. Many disadvantageous side-effects and some accidents have been observed, but I consider this inevitable in view of the powerful action of these agents. The post-cortisone withdrawal syndrome is painful, and failure to obtain complete improvement is often distressing, but nevertheless, a long-continued administration of both cortisone and ACTH can often be successfully accomplished without evidence of toxicity or serious side-reactions.

A continued study of many dosage schemes is needed and we must continue to search for measures to supplement the effectiveness of these hormones.

Despite these unsolved problems, I feel no discouragement, and to me the future looks bright.

DR. DOUGLAS TAYLOR (*Toronto, Canada*): I should like to ask four questions:

First.—I know of one patient who, although under very careful control in hospital, with frequent " negative " *x*-rays of the chest, suddenly developed acute miliary tuberculosis while being treated with ACTH (and cortisone). I want to ask the doctors who presented these papers whether or not it has been their experience that tuberculosis is a dangerous complication; or whether or not they feel that our patient may have been an isolated exception.

Second.—I believe that the best way to relieve pain and prevent deformity in a joint is by the proper use of a splint, combined with heat and the correct type of graded exercise. I should like to know whether attention has been given to protecting involved joints by splinting or bandages.

Third.—We see in the public press accounts of arthritic patients who were " crippled " or " bedridden ", but who got up and danced and climbed ladders after receiving cortisone. I should like to know what happens in such cases to those joints which have been partly destroyed in advanced rheumatoid arthritis. It seems to me that in joints with eroded cartilages, swollen synovial membranes, and distended capsules, much additional damage would be caused. Has any study been made of the effect of this unwonted physical activity upon the damaged joints ?

Fourth.—This refers to a fact already mentioned, that a patient can get ACTH or cortisone outside his own doctor's control. Can a patient go into a drugstore in the U.S.A. and buy cortisone without a prescription ? A few patients have told me that after they had received the drug from a doctor they felt so well that they bought it on their own from a drugstore, and continued to use it without supervision. I think this is a dangerous situation with a drug so powerful, and still in the experimental stages. I am interested to know what type of control there is, if any, of the public marketing of ACTH and cortisone in the United States.

DR. WILLIAM B. RAWLS (*New York*): I should like to emphasize Dr. McEwen's remark, that we should not fear to use cortisone and ACTH, or belittle their value until further information is available. I have had untoward reactions in the past and will most likely have some in the future, but this will not prevent my use of these compounds. I have tried to instill caution but not fear into those who prescribe them.

There are a good many untoward reactions that have not been fully explored in these papers, and I should like to report our experience and also the information obtained by questionnaire on thrombo-embolic phenomena occurring during the use of these compounds. In my series of 100 patients, two developed myocardial infarction, and one thrombophlebitis during therapy. There were eighty replies to the questionnaire, and several hundred cases reported, but the data was insufficient in all except 1,036 cases. Thrombo-embolic phenomena occurred in eighteen patients in this group.

At the spring meeting of the New York Rheumatism Association, Dr. Stuart W. Cosgriff

reported the occurrence of 27 thrombo-embolic phenomena in 21 patients out of 450 treated. There were 1,586 cases in the combined series with 48 (3 per cent.) instances of thrombo-embolic phenomena.

I believe the present recommended dose schedule of 300 mg. the first day, 200 the second day and 100 daily thereafter is too large, particularly in those with hypertension and/or arteriosclerosis, and that it may produce troublesome side-reactions. I believe we should begin with smaller doses and that the maintenance dose should be as small as will enable the patient to carry on a useful life. One should not attempt to maintain these patients quite symptom-free. Our maintenance dose has ranged from 37·5 to 75 mg., being mostly about 57 mg. I do not think we should be afraid, but that we should use a little more caution and adapt the dose to the individual. I should be glad to hear from other members who have had similar experiences.

DR. ROBERT MULLER (*New York*): I should like to ask whether there is any difference in the withdrawal syndromes of cortisone and ACTH.

DR. WILLIAM D. ROBINSON (*Ann Arbor, Mich.*): I should like Dr. Freyberg to tell us a little more about the two patients who developed diabetes during treatment. Did they have glycosuria only or did they also have hypoglycaemia ? Did they develop ketosis ? Did the diabetes persist ?

DR. SMITH (*Youngstown, Ohio*): Was a deliberate attempt made to regulate the sodium and potassium intake ?

DR. HUGO A. FREUND (*Detroit, Mich.*): Is this paper not intended merely as a progress report? We are still at an early stage in this type of therapy, and what we are hearing to-day is a report of what has been done to date. Do the speakers wish us to understand that, when all these various types of cases in many stages are thrown into one hopper, we are to draw general conclusions from their failure or progress ?

I feel that we have lost sight of the intention of the first speakers, who are evaluating the use of the hormones rather than drawing any final conclusions.

DR. BAYLES: I agree, of course, that this is only a preliminary report on the use of high-dosage cortisone therapy.

In our experience with children with rheumatoid arthritis, 200 mg. cortisone daily is not high-dosage treatment. Our two children with Still's disease, who received 400 mg. cortisone daily for 21 days, have remained now in remission for 35 days after stopping treatment. I feel rather strongly that high-dosage cortisone therapy will be useful in acute or chronic rheumatic fever, and I am sure that Dr. Bunim would agree that, even though he gave large amounts of ACTH, it could not be said that this simulated high-dosage cortisone treatment. In using ACTH one can never be sure of the actual circulating 11-, 17-oxysteroid level which is produced.

I should like to comment on Dr. Engleman's remarks on intravenous ACTH, in that patients receiving 500 mg. cortisone a day do not respond to 20 mg. ACTH given over an 8-hour period. It is possible that they would respond to a 24-hour ACTH intravenous infusion.

I agree with Dr. Clark and Dr. Taylor and the others who pointed out that in the proper treatment of arthritis we must not forget the fundamentals of rest and proper joint care, which were used to such great advantage before the days of ACTH and cortisone. Perhaps it would be well to invite Dr. Swaim or Dr. Kuhns to talk to this group next year on orthopaedic management and the use of plaster casts in the care of rheumatoid arthritic joints.

DR. FREYBERG: I feel that some of the discussion centred in a pessimistic interpretation of our paper. I did not wish to give that impression. We set out to evaluate a certain plan of prolonged treatment. A preliminary report was made a year ago, at which time there had been no opportunity of following up these cases. As the title indicates, to-day's report is, as Dr. Freund so well put it, a progress report. Its purpose is to relate what in our experience cortisone will do and not do. I will refer to this aspect again after answering some of the more specific questions.

Dr. Taylor asked about the effect of cortisone on tuberculosis. Everyone should be cautious not to treat a patient who has tuberculosis. There is abundant evidence to indicate that this disease may be unfavourably influenced.

There was a question whether the withdrawal syndrome after ACTH is similar to that after cortisone. Some patients have had similar withdrawal manifestations. We feel that the withdrawal syndrome is not simple prolonged hypo-adrenalism, but is largely due to changes in the connective tissue which has become dependent upon large amounts of cortisone. Thus, even after correction of hypo-adrenalism by the use of ACTH, the syndrome persists until the connective tissue metabolism readjusts itself.

Dr. Robinson asked about the diabetes seen in our patients. I want to emphasize that we

have seen diabetic changes in patients treated with cortisone in more than the two mentioned in this series. This complication has occurred in the early stages of cortisone treatment and the steroid has been discontinued; thus such patients are not included in the group of cases given prolonged treatment. However, we intentionally continued cortisone in two patients in order to study the metabolic changes. When the steroid was discontinued, the diabetes gradually subsided. We think that cortisone will change a latent to a manifest diabetes. However, we were surprised to find that ketosis did not occur, even though in one patient as much as 180 g. sugar was eliminated in the urine daily.

We did not attempt to prevent electrolyte changes; we wished to learn the incidence of such changes, so made frequent observations to study them. When they occurred, we attempted to correct or control them.

I believe I can best summarize the feelings of our research group by recalling to you that in January, 1950, I concluded a paper presented before the New York Academy of Medicine, with the statement that I did not share the pessimism of many investigators regarding the future of the clinical use of cortisone and ACTH in rheumatoid arthritis, but felt it was up to the physicians and the chemists to find out how to put these materials to safe and effective use. I still feel that not pessimism but conservatism is required—because of the limitations that these studies show.

Clinical investigators recognize potentialities of this agent for the benefit of rheumatoid arthritis. Never before has such a potent antirheumatic substance been available, but we need to know better how to use it.

Although we have been disappointed with some of our results, we are not discouraged from our search for satisfactory practical methods of treatment.

DR. SLOCUMB: I agree with Dr. Freyberg's closing remarks. Dr. Hartung mentioned 50 mg. cortisone daily as the top dose for many of his patients. I agree that 50 mg. is the highest daily dose well tolerated by many women in the menopausal or postmenopausal period and also by a few women who are menstruating regularly. However, most men will tolerate daily doses of 62·5 mg. or more without signs of hypercortisonism. For patients with rheumatoid arthritis, large initial doses of cortisone which will produce maximal desired effects rapidly are not necessary and are usually not desirable. It is distressing to hear of patients who after the first day or two of treatment with cortisone or ACTH become euphoric and have so much relief of symptoms that they jump out of bed and jump around the room; we know this euphoric state cannot be maintained for long without development of hypercortisonism, and the patients resent the loss of this exhilaration produced by reductions in dosage. Patients with marked osteoporosis run the risk of fractures during such stimulation.

Cortisone and ACTH cannot be expected to repair damage already done to affected joints, nor can they be expected to control symptoms from over-use of the damaged joints. When significant damage to joints is present, it is best to determine carefully how much of the disability is due to active rheumatoid arthritis and how much to mechanical injury. It is best to place the patient at rest in bed for 1 to 3 days to prevent the over-use of affected joints. Those that remain inflamed and are least affected by the period of rest should be watched carefully in determining the dosage of cortisone or ACTH.

There were several questions regarding libido during administration of cortisone. In our experience there were no instances of decreased libido with small suppressive doses of cortisone.

When small suppressive doses of cortisone were used, supplemental use of potassium salts was not necessary and seldom was it necessary to restrict the intake of sodium chloride.

DR. HENCH: This has been an interesting and instructive afternoon, providing what one might call a " shakedown " session. It is exactly what we must have and will continue to have for many years to come.

I hope no one will take offence at something I should like to say. Some who are now trying to use cortisone or ACTH as therapeutic agents, especially for chronic diseases such as rheumatoid arthritis, are, it seems to me, unduly disturbed by the difficulties of the moment. When the clinical result is excellent and no undesirable effects occur, the physician's spirit rises: " These hormones are wonder drugs ", he says; but in the face of difficulties (when it is not yet possible by present methods of administration to find an adequate dose free of side-effects, or when relapses occur) he becomes prematurely discouraged.

We must not be over eager and impatient in this matter of developing a better, and perhaps a complete, understanding of the physiologic use of cortisone and ACTH, especially in chronic diseases. We lack the basic information to establish a truly physiologic method of administration.

Those who are trying to develop, by trial and error and with concern for calculated risks, a reasonably safe and effective method of administration are to be encouraged. Their labours are so necessary, and have already been surprisingly fruitful.

But in contrast to the harassed "therapists" (whose responsibilities and feelings I share) are those whose objective is not so much a dosage-scheme for to-day, but a basic knowledge of the role of these and related hormones in the pathogenesis of rheumatic diseases. Such investigators, despite the practical pressures of the moment, must collect for us the vital information we now lack: How much endogenous cortisone and ACTH do normal persons develop in health and under stress? how do the peripheral tissues of normal persons or rheumatic patients metabolize endogenous or exogenous cortisone or ACTH?

It has taken many years to reach what might be called "first base", to be able to demonstrate at will the potential reversibility or "suppressibility" of some of these diseased states and to discover agents for the study of this phenomenon. One must not be discouraged if "home plate" has not yet been reached, for I am confident that it will be reached in time.

Degenerative Joint Disease of the Hip (Malum Coxae Senile, Osteo-arthritis of the Hip): Relief of Symptoms following Cortisone Therapy. By RALPH H. BOOTS, and CHARLES RAGAN, *New York*.

Twelve patients with malum coxae senile were treated with cortisone. The early and late therapeutic results of this group were reported.

Discussion.—DR. RUSSELL L. CECIL (*New York*): I have not had much experience with the treatment of osteo-arthritis with cortisone, but we have not limited our work to the hip, but have tried cortisone on osteo-arthritis in the knee and in two cases in the back. One patient who did particularly well was a woman of 72 or 73, who had always enjoyed good health. She took cortisone very well and derived much benefit as far as the hip was concerned, but suddenly developed chills, fever, and pyelitis, which had probably been latent, due to an old stone in the pelvis of her kidney. The interesting sequel was that the pyelitis quietened down, and that under treatment the patient became asymptomatic. However, we did not dare give her any more cortisone, and the hip again became very painful. Thereupon a very animated argument was started between the urologist, the orthopaedist, and the medical men, as to whether she should have a cup operation on her hip. It was finally decided to have the operation, and the result was excellent. She now has a painless mobile hip, and no trouble with the kidney.

DR. JOSEPH HOLLANDER (*Philadelphia, Pa*): We have treated eight patients with osteo-arthritis of the hip with cortisone. As in Dr. Boots' series, most of the patients were of the older age group. We have not been as fortunate as he in results, but we agree with the indications for cortisone therapy in this progressive disease.

In six of our eight cases, we obtained insufficient relief of pain after two weeks' intensive therapy to justify continuing the drug. The two patients who did derive significant relief have not been followed long enough to determine what the long-range effect will be.

We feel, therefore, that while cortisone is worth a trial in malum coxae, it is not the treatment of choice, but rather something to use in severe cases demanding desperate remedies.

DR. SOLOMON P. CARP (*New York*): Our findings in a similar study are in accord with those of Dr. Boots. We observed thirteen cases of advanced osteo-arthritis of the hip, the majority with bilateral involvement. Each had been studied by the orthopaedists and referred to us as serious and difficult problems. The complaints in all cases were severe pain, stiffness, and impairment of motion of the involved joints; *x*-ray films showed advanced degenerative changes and almost total loss of joint space.

With ACTH and cortisone treatment, ten of the thirteen showed considerable improvement, relief of pain, diminution of stiffness, and improved co-ordination of motion. All ten were able to move with greater facility and to perform such simple motions as walking up stairs and arising from a sitting position, but only two showed any significant change in the range of motion of the involved joints.

ACTH and Cortisone in the Treatment of the Shoulder-Hand Syndrome. By JOHN W. SIGLER, and DWIGHT C. ENSIGN, *Detroit, Mich.*

ACTH and cortisone were employed in the treatment of twelve patients of whom six manifested the complete shoulder-hand syndrome and six were classified as acute or

chronic incomplete shoulder-hand syndrome. In most instances small doses (40-60 mg. ACTH or 50-100 mg. cortisone daily for a period of 10 days to 2 weeks) led to good therapeutic results. In some cases pain and swelling were alleviated and normal motion of the extremity established within a few hours. Shoulder-hand syndromes following post-infarction states responded favourably. Once pain had subsided and increased motion had been established, physiotherapy was found useful.

Excellent results were observed in ten of the twelve patients, two experienced relief from pain but did not regain the full range of motion.

Discussion.—DR. SIDNEY S. BERKOWITZ (*New York*): Our findings have been similar to Dr. Sigler's. In eleven cases of reflex dystrophy of the upper extremity treated with cortisone and ACTH, the results compare favourably with those in patients treated with sympathetic nerve blocks. In fact, we observed good results with the use of the hormones in several cases who failed to respond to stellate ganglion blocks. In our small series, somewhat larger initial doses were required for the first 5 to 10 days than those commonly needed in rheumatoid arthritis. So far our results have been impressive, and certainly warrant further study.

ACTH and Cortisone in Periarthritis of the Shoulder (" Frozen Shoulder "). By MORTIMER EHRLICH, SOLOMON P. CARP, SIDNEY S. BERKOWITZ, NORMAN SPITZER, MURRAY SILVER, and OTTO STEINBROCKER, *New York*.

Fourteen cases with chronic symptoms refractory to treatment who were given ACTH and cortisone are considered in three groups:

(1) Eleven treated with these compounds without manipulation; effective treatment in six.
(2) Three of five cases in Group 1 who were unresponsive to the steroids, were subjected to manipulation and the administration of ACTH or cortisone was continued; treatment completely effective in one.
(3) Three received the steroid for the first time after manipulation had been carried out; great improvement and recovery in two.

Nine of the fourteen patients were greatly improved or recovered completely. Maintenance doses were required for a limited time to overcome recurrence of symptoms during attempted rest periods. The trend of responsiveness of periarthritis of the shoulder to ACTH and cortisone without and with manipulation, suggests that further investigation would be worth while.

Discussion.—DR. WILLIAM D. SICHER (*New York*): One of the most difficult problems in evaluating reports of this type is the interpretation of the other man's standards and criteria of what constitutes a serious or advanced case, and also of what constitutes a therapeutic response.

I have had the opportunity of following many of the patients included in the series just reported by Dr. Ehrlich, and should like to sketch one of these briefly:

This patient is a woman who began to develop pain and disability in the left shoulder late in 1948. Within a few weeks her pain was almost constant and the range of motion was limited to 10 or 15 per cent. of normal. During the next year she was seen by at least six physicians of various specialties. Treatment included physical medicine, *x*-ray therapy, local injections at trigger points with alcohol and iodine, other injections at trigger points with procaine hydrochloride, brachial plexus blocks, and several manipulations of the shoulder joint under anaesthesia.

After admission to hospital the patient's condition deteriorated, until she was taking five to six doses of demerol each day. Within 2 to 3 hours of the change from placebos to cortisone, which was carried out successfully without her knowledge, the use of demerol was cut in half. Within a week from starting the cortisone, the demerol had been voluntarily discontinued and function at the left shoulder was rapidly returning toward normal. Within three to four weeks function was almost complete and the patient was pain-free. Cortisone was discontinued shortly thereafter, and the patient has remained well since then. That was almost a year ago.

There were other cases of this general nature in the series just described, and I believe this is what Dr. Ehrlich referred to when he talked about advanced and serious problems.

It would seem that further observations on the effects of cortisone are well warranted in these non-rheumatoid states.

DR. HENRY H. JORDAN (*New York*): The result of manipulation under general anaesthesia for periarthritis or adhesive capsulitis of the shoulder depends to a great extent on the surgeon's

technique. Few, if any, recurrences of adhesions will be found after atraumatic manipulation, but adhesions are much more common when the emphasis is on force rather than on time. The use of cortisone to prevent the formation of adhesions after manipulation seems logical and should be tried whenever possible.

DR. NATHAN R. ABRAMS (*Cincinnati, Ohio*): My series is not large, but my five cases were considerably shorter in duration. All were treated within the first month of their illness with cortisone on an ambulatory basis. Of the five, one showed no improvement at any time; of the other four, one experienced great improvement and maintained it after the cessation of two weeks' therapy, but the other three promptly relapsed and later responded well to other methods, such as *x*-ray therapy and physical therapy. This seems to show that methods other than cortisone should be used in the early stages.

DR. STEINBROCKER: I should like to add that the proportion of early cases in Dr. Sigler's group was higher than in ours, so there will be some difference in our results. Nevertheless, our results coincided very much with his, the difference arising from the fact that all our cases but one were chronic, longstanding examples of the shoulder-hand syndrome.

DR. LYON LAPIN (*Montreal, Quebec, Canada*): Was any difference noted by the investigators of these cases between those in which calcium was found by *x* ray and those in which no calcium was found. As I understand it, Dr. Ehrlich's cases were all ones in which calcium was not seen.

DR. JOHN W. SIGLER (*Detroit, Mich.*): Four of our patients had calcification, but there was only one case of periarthritis that had calcification in the involved side.

DR. STEINBROCKER: None of Dr. Ehrlich's cases of periarthritis showed calcification.

Significance of Giant Follicular Hyperplasia in the Lymphadenopathy of Rheumatoid Arthritis. By A. G. MOTULSKY, S. L. WEINBERG, OTTO SAPHIR, and E. F. ROSENBERG, *Chicago, Ill.*

Lymphadenopathy is frequently encountered in patients with rheumatoid arthritis. Lymphatic system involvement is an integral part of the pathology of Still's disease and may be found in Felty's syndrome. Lymph-node biopsies in a series of patients with rheumatoid arthritis revealed pathological evidence of giant follicular hyperplasia; in some instances this was accompanied by fusion of lymph follicles, a criterion considered to be one of the characteristics of malignancy. Other patients showed follicular hyperplasia not of the giant variety. Serial lymph-node sections in instances of non-specific follicular hyperplasia and true giant follicular lymphoblastoma were compared with similar material from our series of patients with rheumatoid arthritis. While the period of clinical observation of these patients is too short to permit a definitive statement as to the true nature of the lymph-node lesions observed, it is our tentative conclusion that the histologic picture of giant follicular lymphoma (Brill-Symmers disease) may be simulated by the lymph-node lesions found in some cases of rheumatoid arthritis.

Discussion.—DR. WALLACE GRAHAM (*Toronto, Canada*): In 1948, two of our patients with severe rheumatoid arthritis were found to have unusual enlargement of lymphatic glands:

(1) In a male aged 42, some were the size of a small walnut. The biopsy was reported as typical of giant follicular lymphoblastoma.

The differentiation between cortex and medulla no longer exists and a good proportion of the glandular tissue is composed of huge hyperplastic lymphoid follicles with greatly expanded germinal centres with a thin compressed rim of lymphocytes surrounding them. Within the germinal centres mitotic figures are fairly numerous, etc.

A synovial biopsy from the knee revealed the usual picture of rheumatoid arthritis. After deep *x*-ray therapy the glands temporarily diminished in size.

In 1950, biopsy of the glands was again carried out before and after the administration of cortisone. After 3 gm. cortone over 20 days the glands had almost completely disappeared. After cortisone, a large portion of the medulla was found to be replaced by fat. Germinal centres were numerous but small. The biopsy was reported as chronic lymphadenitis.

(2) A male, aged 38, presented a similar picture; the first biopsy was reported as giant follicular lymphoblastoma, and a synovial biopsy from the knee showed no significant lesion. This patient developed a tumour in association with a peroneal tendon. This also was non-malignant. A second biopsy of a gland in September, 1950, was reported as hyperplasia of a lymph node.

Both patients have now been under observation for three years and have shown no sign of malignancy. We feel that these glands represent an unusual hyperplasia in rheumatoid arthritis,

but should agree with Dr. Motulsky that the histologic picture of giant follicular lymphoma may be simulated by the lymph-node lesions found in some cases of rheumatoid arthritis.

Gross Osteopathology of the Arthritides. By WILLIAM J. TOBIN, and T. D. STEWART, *Washington, D.C.*

Gross pathological changes were observed in the arthritides; the material came from the collection of skeletal remains in the Department of Anthropology of the Smithsonian Institution, Washington, D.C. The specimens selected were carefully studied, photographed, and *x*-rayed. Various stages in the calcification of the ligaments of the spine were presented, with examples of complete fusion of the spine, considered to be the end result of an ankylosing type of arthritis of the spine. Degenerative changes with hypertrophic spur formation of the various joints were illustrated. The antiquity of the various types of arthritis was shown in a fused cervical spine from the 12th Egyptian Dynasty (about 2000 B.C.) interpreted as a Marie-Strümpell arthritis. Specimens showed arthritic changes secondary to trauma, postural habits, developmental conditions such as coxa vara, and slipped femoral epiphyses.

Discussion.—DR. DARRELL C. CRAIN, JR. (*Washington, D.C.*): This work deserves commendation from the purely physical aspect. The various museums in Washington contain more dried bones than ever Ezekiel saw in his famous vision. Dr. Tobin is the first who has tried to sort them and to bring some order out of chaos. It has been a tremendous physical task and he deserves the highest praise for the amount of time he has spent on this work.

Little of the material available in the various medical museums is properly catalogued, and little work has been done on the subject in recent years, Dr. Douglas Collins's book being about the only up-to-date study, but work of this sort is essential for a clear understanding of the basic mechanism in the arthritides, and Dr. Tobin and Dr. Stewart have made a valuable contribution.

DR. EDWARD F. ROSENBERG (*Chicago, Ill.*): There is much to be learned from the study of bone specimens, and I hope this work will continue. I should like to call attention to a particular field of study in relation to the pathology of rheumatic diseases, the problem of rheumatoid sacro-ileitis. Clinicians daily observe progressive destructive changes in roentgenograms from patients with rheumatoid spondylitis, but the literature contains no information on the histological nature of these lesions. I hope that the studies described to-day will, as they are continued, throw some light on this subject.

DR. TOBIN: These specimens are quite old and are usually devoid of any soft tissue. Only the mummy specimens show any soft tissue, and even in these it is very difficult to make any study of the changes in the soft tissues.

I regret that time does not permit me to show additional specimens illustrating arthritic changes in the sacro-iliac joint, hip, and knees. Our paper is merely an introduction to this interesting subject. We have at the Smithsonian Institution approximately 20,000 skeletons from various geological and anthropological periods up to the present day, and so far, we have dusted off, so to speak, only the first row in the first room.

Effects of Some 11-Desoxysteroids in Rheumatoid Arthritis. By WILLIAM S. CLARK, HENRIK O. TONNING, JOSEPH A. BLAIS, and WALTER BAUER, *Boston, Mass.*

Forty-five patients received the following 11-desoxysteroids:

desoxycorticosterone,	21-propionate,
" saturated " desoxycorticosterone,	testosterone,
pregnenolone,	dehydroisoandrosterone,
16-dehydropregnenolone,	progesterone,
Δ^5-pregnene 3-(b),	premarin,
21-diol-20-one,	estradiol benzoate.

In one patient, mineral and nitrogen balances were determined during the administration of testosterone, desoxycorticosterone, and cortisone—singly, together, and in binary combinations.

None of the steroids exhibited a significant antirheumatic effect in the dosages used. The mild subjective and objective improvement observed in some patients was no greater

than that noted during the administration of placebos. In all cases the therapeutic results were classified as Grade IV (Steinbrocker).

Desoxycorticosterone and testosterone did not quantitatively or qualitatively alter the antirheumatic effects of cortisone, although testosterone counteracted its effect on protein metabolism. Desoxycorticosterone had no adverse effect on the arthritis even in the presence of considerable salt retention.

These observations further suggest that only carbohydrate active corticosteroids are capable of suppressing rheumatoid arthritis, and they indicate that the antirheumatic effect of cortisone cannot be altered by desoxycorticosterone and/or testosterone.

Discussion.—DR. HOWARD F. POLLEY (*Rochester, Minn.*): Among the group of steroid substances chemically related to cortisone which we have tested at the clinic were six 11-desoxysteroid preparations.* Further data concerning three of these (desoxycorticosterone, Δ^5-pregnenolone, and 21-acetoxy-pregnenolone), are included in Dr. Clark's report. Our results were similar to those which he has reported.

The other 11-desoxysteroid preparations which we tried were 11-desoxycortisone (also known as substance S of Reichstein), 17-hydroxyprogesterone, and pregnenetriolone acetate. None of these preparations revealed any antirheumatic activity.

I concur with Dr. Clark's conclusions, that the 11-desoxysteroids are without antirheumatic activity in so far as we know how to use them at the present time.

DR. WILLIAM K. ISHMAEL (*Oklahoma City, Okla.*): Our preliminary report on the use of testosterone in rheumatoid arthritis was published in September, 1949; follow-up reports were made to the American Rheumatism Association in 1950, and again at the Steroid Conference in Mexico City in January, 1951.

Of the 124 patients who have received large doses of testosterone, approximately one-half have received it for 2 years, and approximately one-half for about 18 months.

At this time, 71 patients (57 per cent.) are still in Grade II remission. In addition to the Steinbrocker classification, we now require at least one year before we give an opinion on the final effects of any substance which is being tested. The above-mentioned 71 patients do not include eight women who were responding satisfactorily, but in whom the testosterone had to be discontinued because of undesirable side-effects.

After observing the effects of testosterone for this period of time, we have again concluded that this drug has no specific action against the inflammatory joint lesion, but is non-specific, exerting beneficial effects through a generalized metabolic influence. However, until a more specific substance has been developed, testosterone will have a place in the management of certain patients with rheumatoid arthritis.

DR. WILLIAM D. ROBINSON (*Ann Arbor, Mich.*): I should like to support Dr. Clark's contention that rheumatoid arthritis is not characterized by an adrenal steroid with excessive salt and water activity. The best means of testing for mineralocorticoid activity is to determine the concentration of electrolytes in the sweat. Using as standards the test methods worked out by Dr. Jerome Conn, we applied this test to rheumatoid arthritis. We found that the sweat concentration covered a wide range, and in no case fell within the limits showing hyperadrenalism, such as Cushing's disease or adrenocortical tumour.

With respect to the antirheumatic effect of the adrenal steroid, I must add an observation which somewhat complicates the picture. We have done some preliminary work with one hormone having definite carbohydrate activity, namely, corticosterone, Kendall's Compound B; we were unable to demonstrate any antirheumatic effect.

DR. WILLIAM R. MERCHANT (*Washington, D.C.*): Dr. Clark stated that testosterone will inhibit or prevent the alteration of protein metabolism without changing the antirheumatic effect. Does he use the term " protein metabolism " alone to refer to the nitrogen-balance studies presented, or does this include albumin/globulin alterations ? If albumin/globulin studies were included, what methods were used ?

DR. JOHN W. GRAY (*Newark, N.J.*): We treated 60 patients with progesterone, giving 200 to 400 mg. intramuscularly daily for 1 to 2 months; 45 showed objective improvement, many complete reversals simulating those from the use of cortisone. They all relapsed when progesterone was discontinued. Then we tried 1,000 mg. orally daily for 1 to 2 months with no result. The

* Polley, H. F., and Mason, H. L. (1950). *J. Amer. med. Ass.*, **143**, 1474.

disadvantages of progesterone therapy are pain at the site of injection and withdrawal bleeding in pre-menopausal women.

We treated 36 patients with pregnenolone, four of whom improved but only subjectively.

DR. W. PAUL HOLBROOK (*Tucson, Ariz.*): One thing must be said in talking of these substances and various other steroids. We have all been guilty of running screening tests on these wholly insoluble substances, such as pregnenolone, when we have no evidence that they are absorbed either by injection or by way of the gastro-intestinal tract.

I believe that before we say that these steroids do or do not possess antirheumatic qualities, we ought to devise some method of determining whether these ordinarily insoluble substances are absorbed.

DR. J. J. BUNIM (*New York*): We studied the effects of desoxycorticosterone acetate on a child with Still's disease who responded very well but manifested the diabetogenic effect of cortisone. We desired to see whether the administration of desoxycorticosterone acetate would

(*a*) have an antirheumatic effect like cortisone,
(*b*) intensify the rheumatic disease,
(*c*) have no effect on the arthritis one way or another (as Dr. Clark reported).

Furthermore, we wanted to know whether DOCA would inhibit the diabetic effect of cortisone.

It was found that DOCA did not affect the arthritis either way, and it did not inhibit the diabetogenic effect of cortisone, but insulin readily brought the glycosuria and hyperglycaemia under control.

DR. CLARK: The ability of testosterone favourably to alter the nitrogen-losing effect of cortisone was first reported by Sprague, and our work merely confirms his.

The question of corticosterone interests me very much. If one examines carefully the evidence that carbohydrate activity is disassociated from antirheumatic activity, one finds it inconclusive. I think the studies with corticosterone from Ann Arbor offer the best evidence that carbohydrate activity is not always associated with anti-inflammatory effects. Our point was that all steroids known to suppress the arthritis have carbohydrate activity.

I agree entirely with Dr. Holbrook's comments. I think it is a very important point that if there is an antirheumatic hormone that does not have these metabolic effects, we want to know it, for it offers considerable hope in the management of the patient.

I also agree with Dr. Holbrook that we have no way of knowing whether these hormones remain in the gluteus muscles for months or are excreted in the faeces when given by mouth.

We have not shown that Dr. Selye's hypothesis is completely wrong, and I think it would be unwise to discard it. We have only indicated that if there is a pituitary hormone producing hormones pathogenic to connective tissue, it does not operate through an electrolyte effect. The remainder of the hypothesis, that there can be a pituitary substance now considered to be growth hormone which can be pathogenic to connective tissue, has not been disproved.

Joint and Muscle Manifestations of Periarteritis Nodosa. By EDWARD W. LOWMAN, *New York.*

Forty-three cases of periarteritis nodosa have been reviewed and joint and muscle manifestations evaluated. In thirty (70 per cent.) of the cases, muscle and joint symptoms were the early complaints; in only four cases, however, was there objective evidence of synovial involvement and in no case was joint involvement a major aspect of the clinical picture. Histological study of synovia showed arterial involvement identical to that seen elsewhere in the disease, with spotty synovial change secondary and proportionate to arterial involvement.

Muscle tenderness and aching were common early manifestations, but in only one case were symptoms suggestive of fibrositis, the muscle symptoms being worse with activity and better with rest. In nineteen there was progression to frank peripheral neuritis.

Discussion.—DR. WILLIAM K. ISHMAEL (*Oklahoma City, Okla.*): It might be interesting to comment on the preliminary diagnoses made on our last three patients with periarteritis nodosa. The first was diagnosed as gouty arthritis, the second as rheumatic fever, and the third as chronic rheumatoid arthritis. Biopsies proved them all to be periarteritis nodosa, which certainly illustrates the variable joint picture. One of these patients who has received ACTH intermittently for 1 year, is still alive.

Postpartum Plasma in Rheumatoid Arthritis and in Patients resistant to Cortisone and ACTH. By LOUIS W. GRANIRER, *New York, N.Y.*

In 1949 it was first reported from our clinic that a sustained remission can be produced in rheumatoid arthritis by the administration of suitable amounts of postpartum plasma. The remission produced is characterized by an improved sense of well being, brighter mental outlook, increased appetite, amelioration of joint symptoms, gain in weight, and restoration to normal of the microcytic anaemia and albumin/globulin ratio. In general, the characteristic response was a striking clinical improvement. There have been no toxic effects and in over 1,000 postpartum-plasma transfusions to date there have been no cases of homologous serum hepatitis. The longest remission after cessation of therapy was 2 years and the shortest 6 weeks.

Discussion.—DR. W. PAUL HOLBROOK (*Tucson, Ariz.*): We have had no experience with postpartum plasma, but we have done some pregnancy blood transfusions. Although, in over 100 cases there appeared to be two or three fairly dramatic results, we discontinued this treatment, primarily because it adds no hope whatever to the ultimate treatment of the thousands of patients with rheumatoid arthritis, since there simply is not enough pregnancy blood available.

DR. B. M. NORCROSS (*Buffalo, N.Y.*): Dr. Lockie and I were very interested in this procedure. We were able to collect postpartum plasma, according to the plan described by Dr. Granirer, and it was administered, in units of 250 ml. at weekly intervals, to six patients with active rheumatoid arthritis. There was no subjective or objective improvement in our patients after each had received a total of twelve infusions, and we were forced to discontinue administration of the postpartum plasma in one patient because of repeated allergic reactions which could not be prevented by antihistamine therapy.

DR. RUSSELL L. CECIL (*New York*): The great problem in the treatment of rheumatoid arthritis is relapses. I wish Dr. Granirer would tell us more about the percentage of relapses, just how severe they were, and how long they persisted.

DR. J. J. BUNIM (*New York*): Dr. Granirer mentioned eight patients who had unfavourable effects from ACTH and cortisone, and responded well to postpartum plasma. It would be of interest to know how many of the patients who failed to respond to postpartum plasma, responded subsequently to ACTH and cortisone.

I have observed two patients who failed to respond to sixteen transfusions of postpartum plasma, but who showed moderate improvement when ACTH or cortisone was administered.

DR. JOHN W. GRAY (*Newark, N.J.*): I should like to ask Dr. Granirer his plan for obtaining large amounts of plasma. We have found it difficult, through lack of co-operation on the part of the obstetricians and lack of interest on the part of postpartum women. To get anything at all, we had to supply twice as much blood as we took away, and then the mother was frequently alarmed to find a transfusion being given; we found more of them were interested in a fancy fee than in transfusion. Unless there is more proof than we now have of some degree of permanent relief, it seems to me too difficult a problem in most communities to obtain sufficient quantities of postpartum plasma.

DR. GRANIRER: We feel the same as Dr. Holbrook; that at present this is a somewhat difficult form of therapy, but no more than insulin in the early days. Whether pregnancy has more or less of the active substance cannot be determined at present. The premise was that during and after delivery there was a sharp increase in hormones which pregnancy might not always possess.

We expect 20 per cent. failures. How long will a patient stay in remission after treatment? Remissions varied from 3 weeks to 2 years. A patient in remission may require treatment every 3 weeks, every month, every 3 months, or at longer intervals.

Patients who do not respond to postpartum plasma therapy may do well with ACTH or cortisone; postpartum plasma is usually beneficial in cases resistant to ACTH or cortisone. We have found that 35 per cent. of patients in the obstetrical ward will donate blood.

Acute Soft Tissue Calcification of Joints other than the Shoulder. By JAMES W. MILLER, ROBERT W. HANF, and JOHN H. WALKER, *Seattle, Wash.*

Calcification of soft tissue, otherwise known as peritendonitis calcarea, tendonitis calcarea, or " bursitis ", may occur near many joints of the body. The most common site is adjacent to the shoulder joint, but many clinicians are not aware that acute soft

tissue calcification may occur in other areas. Specific therapy for this syndrome is so dramatic that an accurate early diagnosis is of utmost importance.

Acute calcifications may also occur at the elbow, wrist, interphalangeal joints of the hand and foot, hip joint, knee, and ankle. We are reporting a series of 31 cases encountered between 1943 and 1950, which have been adequately followed up; in the majority the region of the elbow, wrist, and hip was affected, in the order mentioned. During this same period, 389 cases of " subdeltoid bursitis " of the shoulder were treated; these were mostly acute with demonstrable calcification.

The pathology, symptoms and signs, and treatment of these lesions was discussed. Judicious *x*-ray therapy was considered the best method of management.

Discussion.—DR. GEORGE G. HAYDU (*New York*): Our experience is very much like that just reported. I should like to call attention to the period that precedes tissue calcification; you often find a period of mild complaint and undue stress in the areas of the tendons; inflammation often occurs before calcification, and also, at times, long after *x*-ray therapy. It is well to treat the underlying process in order to prevent any further recurrence.

DR. RUSSELL L. CECIL (*New York*): I had a friendly argument the other day with an orthopaedic colleague, who insisted that they had decided, after years of observation, that *x*-ray therapy had no value in the treatment of these self-limiting bursal conditions in the shoulder. I have always felt that *x*-ray therapy was valuable in acute bursitis of the shoulder and other joints, but the orthopaedist insisted that the radiologists in his hospital were equally convinced that we were deceiving ourselves in using *x*-ray therapy on the shoulder; he thought that the shoulder would get well in a few days anyway, and that we were only wasting our time.

DR. OTTO STEINBROCKER (*New York*): I am inclined to agree with Dr. Miller. I think, however, that the great value of local infiltration of procaine or a related substance, or the two-needle irrigation of the acute calcification, is a valuable procedure that should not be dismissed too lightly. Under ordinary circumstances the most practical procedure, according to our experience in these conditions, is radiation therapy, but when *x*-ray treatment is not available the infiltration of procaine or two-needle irrigation is a valuable technique to dispose of the symptoms and the calcium. They have given us at least as high a proportion of good results as radiation therapy, and have succeeded in some instances when radiation failed.

It is important to appreciate that in what we classify separately as hyperacute, acute, and chronic conditions, the indications are somewhat different. The patient with a hyperacute calcific tendinitis cannot tolerate irrigation or needling while conscious. Such a patient is in too great pain and the local signs are too sensitive and extensive for such a procedure without a simple general anaesthetic, such as a barbiturate intravenously. Usually an injection of morphine or demerol will be satisfactory for needling a merely acute disorder in an ambulatory patient. A chronic condition is not quite as effectively treated, because the chronic symptoms represent a more complex problem, and a calcific deposit in the chronic involvement is merely a roentgenologic sign which may divert us from the true source of the symptoms.

DR. DARRELL C. CRAIN, JR. (*Washington, D.C.*): Those of you who have read the *Rheumatism Reviews* will recall that the last *Review* mentioned that more confusion surrounds the painful shoulder than any other subject, but I think we are beginning to sort out that confusion. The condition discussed by Dr. Miller is certainly analogous to the condition of calcific deposits in the tendons of the shoulder. I should like to suggest that the term " calcareous tendinitis " or " calcific tendinitis " be used; it is a simple descriptive term, and one which could be readily adopted for the condition in or around any joint.

As regards treatment, I agree with Dr. Miller and should like to stress the importance of early *x*-ray therapy. In contrast to Dr. Steinbrocker's experience, my experience with needling has been somewhat disappointing. In the early cases, when needling may be successful, it is often too painful to be tolerated, and *x*-ray therapy is practically always successful; later, when the deposit is harder, needling may be of very little benefit and may serve to irritate the condition.

DR. HOWARD F. POLLEY (*Rochester, Minn.*): I should like to ask Dr. Miller whether he thinks the large calcium formations accumulate within the brief period that the symptoms come on.

DR. MILLER: I am an orthopaedic surgeon myself, and when I develop an acute calcification associated with a joint, I shall choose to have *x*-ray therapy. I have confined my remarks this morning to acute calcifications associated with joints other than the shoulder. I did that because this disease is self-limiting, while in the similar shoulder lesions, where I am sure the pathology

is the same, there is often some residual periarthritis or chronic calcification with symptoms. Regarding the rapidity with which these accumulations appear, it is my opinion that they are frequently present and asymptomatic. Some inadvertent act, such as normal use or over-use of the part, aggravates the situation and the pain arises from mobilization of the calcium. This was Codman's concept of the disease. In most cases, though possibly not all, it has been there quiescent for some time. This theory is supported by the fact that in routine *x*-rays we often see calcific deposits that are asymptomatic.

Sequelae of Adult Rheumatic Fever. By EPHRAIM P. ENGLEMAN, LEO HOLLISTER, and FELIX KOLB, *San Francisco, Calif.*

This report is based on a 6-year follow-up study of 137 unselected veterans who had rheumatic fever in World War II and now reside in the Pacific Coast area. This is the first known study of its kind. Half of the patients had been seen during the war by one of us (E.P.E.). Treatment of the service attacks had been limited to bed-rest and salicylates. The follow-up studies included physical examination and electrocardiographic *x* ray, bacteriologic, psychiatric, and social surveys.

The incidence of recurrences in the past 6 years was low (11 per cent.). Nevertheless, two-thirds of the group experienced unexplained recurrent arthralgia. No instance of so-called " secondary " rheumatoid arthritis of the peripheral joints was seen. However, routine sacro-iliac *x* rays established the diagnosis of rheumatoid spondylitis in three patients with previous *bona fide* rheumatic fever.

Residual heart disease was seen in only 31 patients (22·6 per cent.), all of whom had had carditis during their service attack. With rare exception, cardiac findings were identical with those noted 6 years previously at the termination of their service attack, an observation of prognostic significance.

80 per cent. were leading normal lives, and the remainder showed only slight restriction in physical activity. These and other observations emphasize the favourable outlook of conservatively treated rheumatic fever in the adult.

Discussion.—DR. CURRIER MCEWEN (*New York*): In a study of some children and adults reported some years ago by Dr. De Liee, Dr. Dodge, and myself, the incidence of cardiac involvement was noted in relation to the age at which the rheumatic attacks occurred. We divided the patients in two distinct groups: under 12 and over 25 years of age.

There were 78 children with first attacks of rheumatic fever, of whom 46 showed definite evidence of carditis during the attack, and 28 per cent. showed persisting cardiac damage in follow-up. Among 67 adult patients with first attacks of rheumatic fever, 30 per cent. showed definite evidence of carditis during the attack, but only 7 per cent. showed persistent cardiac damage in follow-up. These figures bear out what Dr. Engleman has just reported. In fact our figures are even more optimistic for the adults than his.

DR. THOMAS MCP. BROWN (*Washington, D.C.*): Many of us have awaited with great interest the results of follow-up studies of these Army rheumatic fever patients, and this is our first opportunity of learning the course of adult rheumatic fever in a large number of patients followed for a significant period of time.

Dr. Swift used to comment that the arthralgias developing in adults who have had rheumatic fever in childhood did not necessarily represent a reactivation of the disease in the usual sense. He would not advise bed rest, was not concerned about carditis, and noted that these cases did well on salicylates. This supports Dr. Engleman's findings.

I should like to ask Dr. Engleman several questions: What was the streptococcic relationship with the onset of rheumatic fever in his adult group ? Was it the same as in the child ? What is his impression regarding dyspnoea ? What was that due to ? Was it an important symptom ?

DR. CHARLEY J. SMYTH (*Denver, Col.*): As you know, the incidence of rheumatic fever in the troops is still quite high, and during the past winter, at the Lowry Air Force Base, we have had the opportunity of collaborating in the study of some 31 young men who are in training there.

The six-year follow-up of men who had acute rheumatic fever during the last war will serve as a yard stick for future study, because they are now receiving carefully controlled courses of ACTH. ACTH was given intramuscularly in fourteen of these patients, and in sixteen it was given by intravenous slow drip for one week and intramuscularly for the next 7 weeks.

The Air Force is greatly concerned about this problem, and I think that Dr. Engleman's observations will enable us to measure what might be accomplished in treating this first or monophasic attack of rheumatic fever in these young adults without the use of hormones.

DR. HOWARD C. COGGESHALL (*Dallas, Texas*): I have had occasion to follow some of these patients through the Veterans' Administration, and I should like to raise one point. The adults with what was apparently rheumatic fever frequently have many muscular symptoms. Whether this is a variation common to adults, or whether it is a characteristic of veterans, I am not sure, but there is a great correlation between compensation and continued symptoms. Even though you find no evidence of heart disease, many of them will still not admit to being completely symptom-free. I think the problem of compensation always makes it difficult to evaluate veterans unless you have objective evidence of definite disease.

DR. ENGLEMAN: Dr. Brown asked about the incidence of streptococcal infection in adults. I must emphasize that this is a follow-up study and that we have no data concerning streptococcal infection before the onset of rheumatic disease. I think, in general, that there was a fairly good relationship between streptococcal infection and the onset of the initial attack.

As far as the dyspnoea was concerned, we felt this was a manifestation of cardiac neurosis.

Dr. Coggeshall's point concerning the difficulty of the evaluation of the veteran who is receiving compensation is an excellent one. However, as far as arthralgia is concerned, we were impressed by the organic pattern. These patients were worse in the morning upon arising and were helped subjectively by aspirin, local heat, and by physical activity. We felt that most of these patients had genuine joint symptoms which were not satisfactorily explained.

Effect of Benemid in Gouty Arthritis. By BERNARD M. NORCROSS, L. MAXWELL LOCKIE, JOHN H. TALBOTT, and CHARLES BISHOP, *Buffalo, N.Y.*

Benemid was administered orally on several different dose schedules to a group of more than 25 patients. Medication was continued over a period of several months. The effects of Benemid upon carefully controlled blood urate observations, upon the frequency and severity of gouty attacks, and upon urate excretion, and its low toxicity was discussed.

In some patients, Benemid was used in conjunction with colchicine and salicylates, while in other gouty patients, it was the sole medicament employed. The effect of Benemid on uric acid metabolism in normal subjects was also mentioned.

It is our belief that Benemid is of value in the long-term control of the disturbed gouty metabolism, and may prevent or minimize the frequency and/or severity of attacks, as well as the complications of this disease.

Discussion.—DR. RICHARD T. SMITH (*Philadelphia, Pa*): We have had experience in fifteen patients with gouty arthritis, having treated them for a period of several months or more. When we first attempted to use Benemid, we used doses of two g. or more a day, and found some patients did not tolerate those doses so well. From experiences in using Benemid with penicillin, it was found that lower doses were successful when there was some renal impairment. Therefore, in gouty arthritis, we tried smaller doses, 0·5 g. daily for a week (one tablet), then increasing the dosage to 1 gr. (two tablets) in divided doses thereafter.

Of the fifteen patients, three had chronic gouty arthritis and six were having increasingly frequent attacks. Nine of these patients had not been adequately controlled with acetylsalicylic acid and sodium bicarbonate, as evidenced by frequent attacks.

In eight of the fifteen patients attacks were precipitated by the therapy; none of these occurred during the first week, when they were receiving only 0·5 g. Benemid daily. The longest period of repeated attacks during the early stages of the Benemid therapy was 10 days. In only one of these patients was it very severe. The shortest period of increased joint difficulty was 3 days, and the average about 6 days.

Maintenance doses of colchicine were continued in four patients; in one of these no increased attacks occurred during the early Benemid therapy; in three there were some mild attacks with the maintenance dose.

Our patients have been warned in advance that they might anticipate some increased joint difficulty during the first few weeks of Benemid therapy. Expecting this, and having been instructed to take their colchicine, as they would for acute attacks in the past, they were well prepared in most instances for relief of their discomfort.

We have also given sufficient sodium bicarbonate to produce alkalinization of the urine, particularly to prevent the possibility of precipitation of urate crystals in the kidney.

We have permitted a liberal diet to the patients throughout treatment, particularly after the first 2 or 3 weeks for those having the greatest amount of difficulty. We had no means of predicting which patients would suffer attacks during the early stages of Benemid therapy, but there is a suggestion that we might expect increased attacks in those whose gouty arthritis had been more severe just before treatment was started.

It may be possible to prevent these increased attacks with the Benemid therapy by giving smaller doses for a longer period. This study we have not yet completed.

One fact is outstanding, that we have a substance apparently superior to anything we have used before as a uricosuric agent, and that with just one to four Benemid tablets a day, many gouty patients are permitted to live an almost normal life with little or no recurrent disability.

DR. LOCKIE: It should be emphasized that we are continually looking for something that will lower the blood uric acid or prevent attacks of gouty arthritis. Here is a substance which has been found to be useful, and relatively non-toxic, and, in Buffalo, it has not precipitated acute attacks of gouty arthritis. I am surprised that Dr. Richard Smith has had so many in his series in Philadelphia.

However, itmust be remembered that we are using 0·5 to 1·0 g. twice a day, in conjunction with other means of treatment, except that the weekly administration of salicylates or cinchophen is omitted. It does not prevent the occurrence of acute attacks, nor does it replace colchicine. In the group we have studied, many patients have been followed for years, so that the pattern of attacks is well known, and it is felt fewer attacks of gouty arthritis have occurred.

DR. WILLIAM H. GOODSON (*Kansas City, Mo*): What is the effect of Benemid on acute gout and are there any complications ?

DR. EPHRAIM P. ENGLEMAN (*San Francisco, Calif.*): What is its advantage over aspirin ?

DR. NORCROSS: In our experience, 1 g. Benemid daily was not as effective as reported by Dr. Smith. We were not able to maintain the maximal reduction of serum urate with this dose unless considerable renal impairment was present. Because of the absence of toxicity, we have continued to use 2 g. daily in the majority of our patients.

Dr. Lockie answered the question about provocation of acute gouty arthritis by Benemid. We have not observed any significant incidence of acute attacks precipitated by Benemid therapy.

We believe that there has been a reduction in the number of attacks of gouty arthritis in this group, although some have had acute attacks after a year of Benemid administration. I think that much more time must elapse before we can make a definite evaluation.

Two patients who developed acute gouty arthritis during Benemid administration were not relieved by larger doses; we employed therapeutic courses of colchicine, and ACTH was used successfully in one patient.

The dosage of salicylates necessary to produce the same continued increase of urate excretion as that observed with Benemid has not been tolerated by many patients. Because there is also a rapid decrease in the salicylate effect on urate excretion with prolonged administration, we have used salicylates in the past on an intermittent, rather than on a continuous, schedule. We believe that Benemid is a better drug than the salicylates because it is not toxic and its effect on urate metabolism is prolonged indefinitely.

Panel Discussion

A panel discussion on " Difficulties and Complications in the Therapeutic Use of ACTH and Adrenocortical Steroids in the Rheumatic Diseases " was conducted by Dr. Philip S. Hench, Chairman, with Drs Edward W. Boland, W. Paul Holbrook, Charles Ragan, and William D. Robinson on the platform.

CHAIRMAN HENCH: Just a word before we start this panel discussion. The papers and discussions of yesterday show that the unjustified hopes and the unjustified fears concerning cortisone and ACTH are rapidly disappearing. The present status of cortisone and ACTH and their application to rheumatic and other diseases is somewhat analogous to the situation which would have occurred had insulin been discovered before we discovered methods for determining the sugar in blood or urine or knew anything about the metabolism of carbohydrates in the normal or the diabetic. Until methods

have been developed whereby one can estimate the quantities of cortisone and ACTH present in blood or bodily tissues of normal and diseased persons, and until we have learned much more than we know now about the metabolism of these hormones, we can only use them therapeutically by a process of intelligent trial and error, by making mistakes and learning from them.

We will discuss first a few questions on rheumatic fever, and on gout, and then proceed to rheumatoid arthritis. The first question is this: How long must cortisone and ACTH be kept up in acute rheumatic fever ?

DR. HOLBROOK: Many patients with acute rheumatic fever show complete subsidence of symptoms after receiving cortisone or ACTH for only a week or 10 days, but others do not. Therefore, in order to provide the maximum chance of preventing cardiac damage, we consistently give the hormones for 4 weeks.

CHAIRMAN: Dr. May Wilson—who uses, as I think you know, one or the other hormone for only one week—told me this morning that her excellent results largely depend on the fact that she can get her " pedigreed " patients, already under general observation, very early, and can start treatment within the first 2 to 4 days of the attack. Dr. Holbrook, have you any comment on Dr. May Wilson's plan ?

DR. HOLBROOK: None, except that the recurrences that develop in some of our patients when treatment is discontinued at the end of a week seem to us more hazardous than the continuous administration of the hormones for a longer period.

CHAIRMAN: Is heart failure with oedema always a contraindication to the use of cortisone and ACTH in acute rheumatic fever ?

DR. HOLBROOK: No, it is not always a contraindication. But it should be carefully borne in mind that low sodium intake, and other means of preventing the accumulation of electrolytes and fluid, should be used in acute rheumatic fever with heart failure.

CHAIRMAN: Do you use diuretics and salt restrictions routinely in rheumatic fever ?

DR. HOLBROOK: Not unless heart failure is present.

CHAIRMAN: We will now turn to gout. Are cortisone and ACTH any better than colchicine ? If so, which is the better, cortisone or ACTH ?

DR. ROBINSON: I believe that colchicine, as it is customarily used, will take care of perhaps 90 per cent. of acute gouty attacks. For those patients who do not respond to colchicine, ACTH offers an excellent treatment. We believe that the dose of ACTH must be large, 100 mg. a day of a long-acting, or up to 200 mg. per day of short-acting, preparation. It must be combined with colchicine, and colchicine in maintenance doses (two to three tablets a day) should be continued for a while to prevent the occurrence of a " withdrawal attack ". In our experience, cortisone has not been as satisfactory as ACTH in the treatment of acute gouty arthritis.

CHAIRMAN: Are cortisone and ACTH useful in chronic gouty arthritis ?

DR. ROBINSON: I don't believe anyone has had enough experience to justify any statement.

DR. BOLAND: Our experience with cortisone and ACTH in the treatment of chronic gouty arthritis has been limited to a few cases. In general we are not convinced that these substances will produce persistent relief of chronic articular disability over long periods, and we are not sure that their uninterrupted use actually lessens the number of acute recurrent attacks. I agree with Dr. Robinson that ACTH is a good adjunctive measure if colchicine fails, but in the usual case of acute gouty arthritis we prefer colchicine to either cortisone or ACTH.

CHAIRMAN: Now we have a few general questions.

What about ACTH peptides ? Are there any prospects for their synthesis in the near future ? Will they be made effective and easier to use than now ?

DR. RAGAN: It will be difficult to synthesize an ACTH peptide. These peptides have been found to be of rather high molecular weight, and in our experience so far, there has not been much difference between the peptides and whole ACTH.

CHAIRMAN: Should the use of cortisone and ACTH still be considered more or less experimental ?

DR. RAGAN: I personally don't think so, but I do think that they should be used with considerable caution and conservatism. I don't think they should be considered experimental in the sense that you don't know what will happen. Their use is still "experimental" if one is considering what the results might be after a 5-year period.

DR. BOLAND: Regardless of how we feel about it, and irrespective of whether we think these hormones should be used only as experimental tools, the fact is that cortisone and ACTH are both on the market and are being employed as treatment agents. It is important, therefore, that we face this reality and strive to find, as quickly as possible, safe and effective methods of employing them in the practical management of patients.

DR. ROBINSON: My viewpoint coincides with those of Drs. Ragan and Boland. The ultimate place of these hormones in the practical management of arthritis, we certainly do not yet know, but I do believe that in the last two years we have been able to discredit some of the fears concerning them. It is also necessary to discredit some of the hopes, but we do know that a significant percentage of patients can be given these hormones safely and effectively for a considerable period.

CHAIRMAN: May I say a word. We have been using cortisone and ACTH at the Mayo Clinic mainly as tools for research, trying to find out, first of all, something about the reversibility of rheumatoid arthritis. That is still our main concern. But the many rheumatologists and other physicians who are now trying to develop a useful, if empiric, method of treatment, are making a splendid contribution. Physicians must try to find out to what extent these hormones can be used now as a safe and effective form of therapy as well as improved methods for their future use.

Next question: What are the chances that long-continued use of cortisone and ACTH will induce irreversible damage to the adrenals?

DR. HOLBROOK: The evidence is fairly clear now that after the prolonged administration of these hormones (e.g. after a year or more of cortisone) the adrenal recovers sooner or later, generally sooner.

DR. BOLAND: That is our belief also. As was stated yesterday, we have given cortisone uninterruptedly for periods up to 14 months and have then withdrawn it. After withdrawal, adrenal cortical function, as indicated by various tests, has recovered in every instance, although in one case it took the eosinophil response as long as 90 days to return to normal.

CHAIRMAN: We now pass on to the subject of rheumatoid arthritis. What are the most common side-effects you have encountered from the use of cortisone and ACTH in rheumatoid arthritis?

DR. HOLBROOK: The short-term usage of these hormones presents no particular problem as regards the development of side-effects, but after prolonged administration of cortisone and ACTH, about 50 per cent. of our patients have developed one or more of the following: round face, oedema, excessive mental stimulation, tachycardia, fatigue, dyspnoea, and so forth. But we do not necessarily stop the medication upon the appearance of any of these findings. In my opinion a daily record of the patient's weight is the best indication whether matters are progressing safely. Excessive gain in weight may be the first indication of trouble.

DR. RAGAN: One point that has not been mentioned much is the appetite of patients receiving the hormones. They consistently gain weight, even without retention of fluid, and it is difficult to keep their weight in reasonable bounds. This is one of our major difficulties, especially if the patient is a young girl who does not want to be a fat girl.

DR. BOLAND: It is our practice to limit the caloric intake as soon as the patient approaches an optimal body weight. Because cortisone and ACTH apparently increase the absorption and utilization of fats and cause increased appetite, it is very difficult to effect weight reduction during treatment if excessive gains have already been allowed.

DR. ROBINSON: The frequency and severity of these adverse manifestations is very definitely related to dosage, as was well brought out in the previous discussions. Sex and age are also important factors in the liability of patients to develop the common side-effects.

CHAIRMAN: Are the side-effects which may result from cortisone different from those which may result from ACTH?

DR. BOLAND: They are essentially the same, although in our experience retention of salt and water and arterial pressor effects are more prone to develop with ACTH than with cortisone.

CHAIRMAN: How often do you have to use special precautions (limitation of salt;

salt-free diet; diuretic) to prevent or control oedema ? Do you use any of these routinely or not until oedema has developed ?

DR. BOLAND: One can go ahead with routine treatment until oedema occurs, and then restrict the intake of salt and/or administer saline or mercurial diuretics. We prefer, however, to place patients routinely on a salt-poor (not a salt-free) diet whenever large or relatively large doses of cortisone or ACTH are being used. This has been valuable during the early phases when large suppressive doses of cortisone or ACTH are employed, and by taking such precautions we believe that oedema is often prevented from occurring. In general, when maintenance doses larger than 50 mg. cortisone a day are being given, the intake of salt is routinely restricted; when this is done it is seldom necessary to resort to diuretics.

The appearance of oedema during treatment should not necessarily serve as an indication to stop cortisone. It is, however, an indication to institute the measure just described and/or to reduce the dose of the drug.

CHAIRMAN: What is the best way to prevent undesirable effects from cortisone or ACTH in rheumatoid arthritis ? What should be one's general policy ?

DR. RAGAN: It is best to undertreat rather than to overtreat the patients. Most of the undesirable results are directly related to excessive dosage. I do not yet know how to predict the development of major mental reactions, although some investigators believe that irritability in the patient is a danger signal.

CHAIRMAN: How much and what do you tell a rheumatoid patient before you begin to use cortisone or ACTH ?

DR. HOLBROOK: To begin with, I make it plain that the hormones are not *per se* a cure, and that other things are also useful. Once a decision has been made to use cortisone or ACTH, the patient must be prepared and willing to take it and able to afford it indefinitely. In my opinion, nothing is to be gained by short-time relief. My goal is to provide a significant amount of relief with a minimal dose. I aim not at the maximal degree of remission which maximal doses will provide but at the greatest improvement from the smallest dose.

CHAIRMAN: What are the absolute and the relative contraindications to the use of these hormones ? Should they be used in the presence of tuberculosis, peptic ulcers, diabetes, psycho-neurosis, a positive Wassermann, amyloidosis, " abdominal pain ", and so on ?

DR. HOLBROOK: There are only two conditions which I consider great contraindications—tuberculosis and diabetes. I am not yet willing to say that they are absolute contraindications if certain other precautionary measures are taken.

DR. BOLAND: I cannot comment on tuberculosis because we have not observed reactivation of a pre-existing lesion in any of our cases, but I can give an opinion on diabetes. For a time glucose tolerance tests were done on every patient who was a candidate for cortisone. Only two patients with normal pretreatment tolerance curves have shown evidence of decreased tolerance to carbohydrates during treatment; in both of these the glycosuria was easily controlled with simple restriction of carbohydrate in the diet.

One of our first patients to receive cortisone was a diabetic whose disease was being controlled by diet and 10 units of insulin a day. Within 48 hours of starting cortisone there was a five-fold increase in the insulin requirement and this increase persisted throughout an 8-day period of treatment. However, the insulin requirements returned to the pre-cortisone level within 48 hours of discontinuing the drug. This indicates that although cortisone accentuated the diabetic state, this accentuation was temporary. Since that time we have treated three rheumatoid patients with pre-treatment latent or mild diabetes mellitus; each of them has received continuous cortisone therapy over a period of many months, and in each instance we were able to control the diabetes satisfactorily—in two by diet alone and in one with diet and moderate doses of insulin.

Mild or latent diabetes is thus not necessarily a contraindication to the use of cortisone, whereas more severe diabetes probably is. One must weight the relief to be obtained against the potential dangers. Knowing that any accentuation of the diabetes will be temporary, a cautious trial of cortisone in mild cases would seem justified.

DR. RAGAN: Latent or obvious tuberculosis is a contraindication. Drs. Knowlton and Perera have had experience with the treatment of Addison's disease and tuberculosis, and we agree with Dr. Thorne and Dr. J. S. L. Brown, that, if you make the organism euadrenal, tuberculosis may be controlled; but if, to achieve a beneficial effect, you have to produce hyperadrenalism, tuberculosis

is a real contraindication. We have had one case of tuberculosis in an Addisonian who has done extremely well on cortisone since we attempted to produce euadrenalism and not hyperadrenalism.

The second major contraindication is a history of psychosis. If a person has had a psychotic episode, we feel the chance of developing a second psychotic episode on cortisone is very great.

DR. ROBINSON: Most of the contraindications are relative. It is a matter of weighing what the patient has to gain against the possible difficulties, the potential response to other forms of treatment, and your own ability to regulate the complicating disease.

I am apprehensive about the use of these hormones in patients with a previous history of peptic ulcer, because I do not know how to detect an early reactivation of an ulcer under cortisone or ACTH, and because of the rapidity with which disastrous complications can occur.

CHAIRMAN: We have treated a few rheumatoid patients who have had inactive duodenal ulcers, so far without any untoward effects. But we consider a peptic ulcer to be an important relative contraindication, and we watch such cases much more closely. Whether we use cortisone depends on the severity of the disease, and the risk is always explained to the patient.

DR. BOLAND: Within the past three months I have seen two patients in consultation who had developed convulsive seizures during ACTH therapy. Both patients had had typical epilepsy in the past and I would suggest that a history of epilepsy might serve as a contraindication.

CHAIRMAN: What is the incidence of rebound reactions after hormonal withdrawal?

DR. ROBINSON: Probably the best available figures are those which were presented by Dr. Freyberg. I believe that, of his 47 patients, five developed severe relapses after withdrawal of cortisone. Our experience has not been so extensive, but relapses can be severe, and they are likely to be a little more severe with sudden cessation of dosage, particularly of oral cortisone.

DR. HOLBROOK: I have found that cessation of oral cortisone is followed by exacerbations much more often than was reported. At least half of our rheumatoid patients developed a severe exacerbation when the oral cortisone was discontinued.

DR. BOLAND: We have seen more rebound relapses than Dr. Freyberg, less than Dr. Holbrook.

DR. RAGAN: We cannot be sure whether the withdrawal attacks represent a rebound or a natural progression of the disease, or whether the patient is worse than he would have been.

CHAIRMAN: How often do cortisone and ACTH lose their effect when dosage is unchanged? Does this happen more often or sooner with ACTH than with cortisone?

DR. RAGAN: I think that many so-called relapses are due to a natural progressive increase in the severity of the disease. Dr. Holbrook suspects that the thyroid has something to do with these exacerbations, and that secondary hypothyroidism sometimes develops, making the cortisone temporarily less effective. When rheumatic symptoms increase during the use of a previously satisfactory dose of cortisone or ACTH, we try to modify the severity of the disease, first by increasing the dose; secondly, by decreasing the physical and emotional activities of the patient.

CHAIRMAN: If a patient develops some intercurrent infection while on a maintenance dose, should one alter the dose? Should one take any special precautions?

DR. HOLBROOK: When a slight cold develops no alteration of the dose and no special precautions are needed. If a major infection develops, we do not alter the dose of the hormone but we may need to use antibiotics also. Sometimes during a course of hormone therapy an infectious process develops very insidiously and fails to give localizing symptoms. The patient may experience nothing but weakness, and, if you take the temperature faithfully, you may find a low-grade temperature. But if you give antibiotics to such a patient he will improve rapidly.

CHAIRMAN: If a rheumatoid patient has recovered from a mild stroke, are cortisone and ACTH safe, and which is safer?

DR. BOLAND: Again one must weigh the benefit against the danger. If the patient's arthritis is so crippling and so uncomfortable that life is miserable, and if his expectation of life is not too long anyway, one should consider employing these drugs cautiously. We have had three deaths during prolonged cortisone treatment—two from acute coronary thrombosis and one from a cerebrovascular accident. All of these occurrences were in older persons, and whether the increased physical activity made possible by the drug may have influenced the course of events or whether the episodes were coincidental we cannot be sure.

I should like to stress one complication which has been very disturbing to us and which has so far occurred only in elderly patients receiving large or relatively large doses. Three patients

developed spontaneous fractures during cortisone therapy; two of these were compression fractures of the lower dorsal spine and the other a fracture of a femoral neck. In view of the fact that spontaneous fractures are not uncommon in patients with Cushing's disease, we believe that this complication may be related to cortisone therapy—to us it appears likely that osseus demineralization may have been accelerated by the induced state of hypercortisonism. The possibility of this complication must be kept in mind in considering cortisone or ACTH therapy in older patients with evidences of skeletal osteoporosis from senility and from rheumatoid arthritis.

CHAIRMAN: Is thrombophlebitis ever a definite side-effect from cortisone or ACTH ?

DR. ROBINSON: The occasional development of thrombophlebitis during or ofter the use of these hormones raises the question whether it is related to the treatment or is co-incidental. We have been somewhat concerned about this, because we had four cases of thrombophlebitis among our first thirty patients. In each instance, the thrombophlebitis developed when the dosage was being decreased or had just been discontinued. Two instances were in patients in whom thrombophlebitis might be expected, one being a recurrence at the site of a previous attack 2 years before. The other two instances were in young people and the circumstances were rather unusual.

We have heard some statistics at this meeting which place the incidence of thrombotic occurrences during hormonal therapy between 1·7 and 2·1 per cent. Has anyone any figures of the incidence of thrombophlebitis in rheumatoids who have not received cortisone or ACTH ?

CHAIRMAN: When the members of the panel were talking about this last night, none had any statistics on the " natural occurrence " of thrombophlebitis among rheumatoid patients.

Among our early patients who received cortisone or ACTH, two developed thrombophlebitis when we were withdrawing or had just withdrawn cortisone, and we became somewhat concerned. Then we were about to begin giving cortisone to another patient on a Monday, but that particular patient developed thrombophlebitis on the Saturday before. So we do not know the final answer.

Next question: How often do cortisone and ACTH produce significant hypothyroidism?

DR. ROBINSON: That depends on how you define the term " significant ". In our experience, some 85 per cent. of patients with rheumatoid arthritis on cortisone or ACTH have shown laboratory evidence of decreased thyroid function, as indicated by determinations of protein-bound iodine and the radio-active iodine uptake. Under ACTH and cortisone treatment, the basal metabolic rate is not reliable as an index of thyroid hypofunction.

In our experience, all the cases of elevation of blood cholesterol reported as a complication of prolonged treatment have been associated with evidences of hypothyroidism; the hypercholesterolaemia is corrected by the addition of dessicated thyroid. If it is asked from the practical viewpoint, how often is it necessary to add thyroid to maintain the clinical effectiveness of these hormones, I must reply that to date, we have seen no patient who required added thyroid to maintain the therapeutic effectiveness of cortisone. Others, however, have reported seeing such patients. We have observed four out of nineteen patients in whom thyroid supplementation was clearly necessary in order to maintain the therapeutic effect of ACTH, and in other patients, on either hormone, we have seen correction of minor clinical and laboratory aberrations.

CHAIRMAN: What symptoms first suggest an impending psychic reaction ? If they appear, must one always stop the hormone ?

DR. RAGAN: As I mentioned before, I think that evidences of over-stimulation, notably excessive mental activity, may suggest an impending psychic reaction.

The major psychopathic reactions that we have seen came as complete surprises. The electroencephalogram is of little value, since encephalographic abnormality may not be correlated with an abnormal mental reaction. If a patient develops a major psychosis, we certainly stop the hormone; but we do not know how to predict such a development.

DR. HOLBROOK: Nor do I know how to choose between the patients who will have psychic disturbances and those who won't. I think if the patient is watched closely, one will note that a mood of depression often precedes a major psychic reaction.

DR. RAGAN: How closely are you going to watch the patient ?

DR. HOLBROOK: It is impossible to watch all of them closely. I agree with that. On the other hand, if you ask the patient to report his moods or changes in mood, you may get some warning.

CHAIRMAN: Assuming you are decreasing rather than increasing dosage, have you any comment on the time limit within which major psychic reactions are or are not likely to occur ? If you have no psychic reaction within a few days or weeks, are you safe ?

DR. RAGAN: I don't think so. Our last suicidal attempt was after 4 months of therapy; this patient had previously had a manic reaction but we did not think she would develop it again. At present, therefore, we should not give the hormones to such a patient.

DR. BOLAND: Our climate in California is so happy, that we have had no such difficulties.

CHAIRMAN: Our psychiatrists have seen most of our patients and have done personality appraisals in many cases before we gave the hormones. Their reports have been gratifyingly accurate in telling us what sort of reaction we might meet in any nervous or unstable rheumatoid patient.

Additional Papers

Cortisone in the Treatment of Osteo-Arthritis of the Hips. By CHARLES Y. BROWN, RALPH A. JESSAR, and JOSEPH L. HOLLANDER. *Philadelphia, Pa.*

Peptidase Levels in Synovial Fluid and Serum in Rheumatoid Arthritis and other Rheumatic Diseases. By JOSEPH J. BUNIM, MORRIS ZIFF, JEROME SIMSON, DENYS K. FORD, and ALFRED SMITH, *New York.*

Observations on the Metabolic and Anti-Inflammatory Effects of Desoxycorticosterone, Testosterone, and Cortisone in a Patient with Rheumatoid Arthritis. By WILLIAM S. CLARK, WALTER BAUER, ELIZABETH L. MANNING, and JANET E. APPLETON, *Boston, Mass.*

Tendinitis (Bursitis) in the Shoulder. By AUGUSTUS M. DAVISON, *Hot Springs, Ark.*

Treatment of Rheumatoid Arthritis by New Methods of Physical Medicine. By JOSEPH ECHTMAN *New York.*

Long-Term Treatment of Rheumatoid Arthritis with Cortisone. By EPHRAIM P. ENGLEMAN and MARCUS A. KRUPP, *San Francisco, Calif.*

Effect of ACTH and Cortisone on the Erythrocyte Sedimentation Rate and Fibrinogen Content of Plasma. By GEORGE R. FEARNLEY and JOSEPH J. BUNIM, *New York.*

Aspects of Blood Protein Changes in Rheumatoid Arthritic States. By HUGO A. FREUND, C. S. STULBERG, ABNER ROBINSON, and DANIEL H. BASINSKI, *Detroit, Mich.*

Stellate Ganglion Block for Acute Subdeltoid Bursitis. By EVERETT J. GORDON, *Washington, D.C.*

Common Emotional Background and Coincidence of Osteo-Arthritis and other Articular and Non-Articular Musculoskeletal Disorders. By JED H. IRVINE, *New York.*

Pathology of Early Articular Lesions in Rheumatoid Arthritis. By J. PETER KULKA and DOUGLAS BOCKING, *Boston, Mass.*

Intra-Articular Injection of Acid Potassium Phosphate in the Treatment of Chronic Arthritis. By JOSEPH J. LANKIN, *Hartford, Conn.*, and R. H. FREYBERG, *New York.*

Effect of ACTH on Acute Disseminated Lupus Erythematosus. By FREDERIC A. LESTINA, DAVID E. MARKSON, SMITH FREEMAN, and PAUL S. RHOADS, *Chicago, Ill.*

Studies of Transmission of Rheumatoid Arthritis to Humans. By WALTER J. LEVINSKY, and JOHN LANSBURY, *Philadelphia, Pa.*

Response of the Schoenlein-Henoch Syndrome to ACTH: Report of a Case with Serial Biopsies.* By JOSEPH E. LEVINSON, MARK HORWITZ, J. PETER KULKA, LOT PAGE, and WALTER BAUER, *Boston, Mass.*

Facial Pains and Headaches Caused by Disco-Osteophytic Lesions of the Cervical Spine. By E. NEUWIRTH, *New York.*

Effects of Intravenous as compared with Intramuscular ACTH in a Selected Group of Patients. By BERNARD M. NORCROSS, L. MAXWELL LOCKIE, JOHN H. TALBOTT, and WILLIAM H. GEORGIE, *Buffalo, N.Y.*

Effect on the Adrenal Glands of Prolonged Administration of Cortisone—Clinical and Animal Studies. By M. PATTERSON, R. H. FREYBERG, and H. SEIGEL, *New York.*

Alterations in Articular Physiology induced by Cortisone and ACTH. By MARIAN W. ROPES, JANET E. APPLETON, and ELIZABETH L. MANNING, *Boston, Mass.*

Rheumatoid Spondylitis with Pregnancy. By CHARLES L. STEINBERG, *Rochester, N.Y.*

Practical Importance of Diurnal Variations in Number of the Circulating Eosinophils. By J. NORRIE SWANSON, *Boston, Mass.* (introduced by DR. MARIAN W. ROPES).

Body Water, Body Chloride, and Plasma Volume Changes in Patients receiving ACTH Therapy. By MORRIS ZIFF, JEROME SIMSON, and JOSEPH J. BUNIM, *New York.*

* Published in full in the September issue of this Journal (*Annals of the Rheumatic Diseases*, 1951, **10**, 255).

ABSTRACTS

This section of the ANNALS *is published in collaboration with the three abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, ABSTRACTS OF WORLD SURGERY, OBSTETRICS AND GYNAECOLOGY, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Sciatica; Gout; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section " ACTH, Cortisone, and other Steroids ", which appears for the third time in the present issue, includes abstracts and titles of articles dealing with steroid research, which although not directly concerned with the rheumatic diseases, may make an important contribution to knowledge of the scope and *modus operandi* of steroid therapy.

Acute Rheumatism

Death Toll from Rheumatic Fever in Childhood. WOLFF, G. (1951). *J. Amer. med. Ass.*, **145**, 719. 1 fig., 13 refs.

The mortality from rheumatic fever and its consequences in children aged 5 to 19 years in the U.S.A. was assessed by adding the deaths from all forms of heart disease to the deaths from acute rheumatic fever. By combining the average number of deaths for 1939-41 with the census figures for 1940, analysis according to age, sex, race, and geographical division has been made. The mean death rate in this period was 11·7 per 100,000, the mortality increasing with age. In general, girls showed a higher mortality than boys, except in the 15-19 age group of white children. The mortality among white children was lower than among non-white children at all ages. Geographically, the mortality was lowest in the southern and highest in the north-eastern divisions.

Mortality rates for the whole population were determined up to 1948. They showed a steady decrease to about two-thirds of the 1939-41 level. The sex, race, and geographical distribution of deaths from rheumatic disease of the heart show many similarities with deaths from tuberculosis and suggest that, as in that disease, social and economic factors are important. *M. Lubran.*

Dehydration Treatment of Rheumatic Fever. COPEMAN, W. S. C., and PUGH, L. G. C. E. (1950). *Lancet*, 2, 675. 3 refs.

It has been suggested that salicylates owe their good effect in rheumatic fever to a reduction of the water content of the body cells. This hypothesis would be strengthened if similar results were obtained by dehydration alone.

Seven male patients with rheumatic fever were subjected to a course of treatment which included limitation of fluids, sodium sulphate by mouth, and intravenous hypertonic saline. Within 24 hours signs and symptoms were reduced, and side-effects were noted similar to those occurring during massive salicylate therapy.

David Nicholson.

Salicylamide: Pharmacology, Fate and Clinical Use LITTER, M., RUIZ MORENO, A., and DONIN, L. (1951). *J. Pharmacol.*, **101**, 119. 4 figs, 5 refs.

In view of the undesirable side-reactions that often limit the use of the salicylates it was decided to investigate further the effect of salicylamide on laboratory animals in preparation for a clinical trial of the drug in acute rheumatism and other types of arthritis. Depression of the central nervous system and paralysis were produced in guinea-pigs, rabbits, dogs, cats, and mice, by a dose of 0·1 to 0·25 g. per kg.; double this dose caused narcosis lasting for 1 to 2 hours, and doses of 1·0 to 2·0 g. per kg. resulted in death from respiratory paralysis. The amide was given by the oral, intraperitoneal or intravenous route. Hypotension observed in the effective dose range was the result of peripheral vasodilatation and not of depression of the heart which, however, occurred after very high doses. In mice the LD50 was 0·313 g. per kg. These observations led the authors to the conclusion that salicylamide is a depressant, whereas the salicylates are more or less stimulant.

By determination of the minimum quantity of salicylamide necessary for analgesia in 90 rheumatic patients it was decided that the average effective and safe dosage was 2 g. every 4 to 8 hours day and night. The results of a trial on 118 patients suffering from a variety of rheumatic conditions showed that there was a marked analgesic effect in 50·8 per cent., a moderate effect in 25·4 per cent., a doubtful effect in 6·8 per cent. of cases, while 17 per cent. of patients had no relief. Of seven patients with rheumatic fever, in six marked relief from pain was noted. The prothrombin time was shortened by salicylamide, whereas with salicylate administration it is lengthened. The toxic symptoms were dizziness in 22 per cent., drowsiness in 7·6 per cent., nausea in 5·9 per cent., and heartburn in 3·4 per cent.; anorexia and diarrhoea each affected one patient. Excretion studies were attempted, but difficulties in the analysis of salicylamide were encountered, as the amide does not hydrolyse readily. It was concluded that salicylamide is useful in rheumatoid conditions and is better tolerated than salicylates.

R. Hodgkinson.

"Growing Pains": a Clinical Study of Non-arthritic Limb Pains in Children. NAISH, J. M., and APLEY, J. (1951). *Arch. Dis. Childh.*, **26**, 134. 7 refs.

As the result of a study of 721 children the authors found non-arthritic limb pains present in 4·2 per cent. of the Bristol school population. These occur most frequently between the ages of 8 and 12 years, with no significant sex difference, but a family history of rheumatic disorders is much more frequent in affected children than in the controls. There are two main categories: (1) diurnal fatigue pains, associated with exertion, postural defects, fatigue, and emotional disturbances, and with a strong family history of rheumatic disorders; (2) paroxysmal nocturnal pains in children without these associations but with similar pains in other members of the family. In a small group of children the pains were an expression of psychological difficulties only. An analysis of 54 hospital patients with similar pains agreed with these findings. Organic lesions were only rarely present. *Winston Turner.*

Traumatic Periostitis in Young Children. BARMEYER, G. H., ALDERSON, L. R., and COX, W. B. (1951). *J. Pediat.*, **38**, 184. 4 figs, 16 refs.

The authors describe what they regard as a common paediatric occurrence—namely, the "acute limping leg" of early childhood. In this condition, after an apparently trivial injury, a radiograph taken 3 or 4 weeks later will often show some ossification of the periosteum at the site of the injury. When the child is *x*-rayed during the acute pain, nothing abnormal is found; but if *x*-rayed when symptoms have subsided, this evidence of ossification will now be apparent. The authors regard this condition as the result of mechanical separation of the periosteum by injury. They supply an academic discussion of all the possible causes which might otherwise stimulate this condition. *John Charnley.*

The Reaction of Human Serum with a Quaternary Ammonium Salt: Results of a Serial Study in Acute Rheumatic Fever. JACOX, R. J., and GALE, R. G. (1951). *J. Lab. clin. Med.*, **37**, 728. 7 figs, 8 refs.

Splenic Enlargement in Congestive Heart Failure and Active Rheumatic Infection. IBRAHIM, M., SOROUR, A., and ELSHERIF, A. (1951). *Brit. Heart J.*, **13**, 212. 10 refs.

The Recognition of the Early Manifestations of Rheumatic Fever. GABLE, G. P. (1951). *Mississippi Dr.*, **28**, 408.

Acute Rheumatic Fever in Uncommon Sites. REICH, N. E. (1951). *Amer. Practit., Phila.*, **2**, 328. 37 refs.

500 Patient-Years of Rheumatic Disease in Children. HIGGONS, R. A., HYDE, G. M., and MALSCH, M. L. (1951). *N.Y. St. J. Med.*, **51**, 1143. 7 figs, 7 refs.

The Treatment of Rheumatic Fever in Children with Sodium Salicylate. (Contributo alla terapia con salicitato di sodio dell'infezione reumatica nell' infanzia.) PELLEGRINI, U., and ORLANDI, E. (1951). *Omnia therap., Pisa*, **2**, 159. 7 figs, 32 refs.

Disturbances of the Heart's Rhythm in the Rheumatic Syndrome in Children. (Zaburzenia miarowości serca w zespole reumatyzującym u dzieci.) CHROSCICKI, A. (1951). *Polskie Arch. Med. wewn.*, **21**, 1. 14 figs, 70 refs.

Rheumatic Infection in Childhood, Rheumatic Carditis. (Über die rheumatische Infektion im Kindesalter, insbesondere die rheumatische Karditis.) KUNSTLER, S. (1951). *Med. Welt.*, **20**, 1025.

The Use of Heparin in Rheumatic Fever. (L'Utilisation de l'héparine dans la maladie rhumatismale.) NORY, J. (1951). *Gaz. med. France*, **58**, 639. 4 refs.

The Absorption and Excretion of Salicylamide given by Mouth and Percutaneously. (Über die Aufnahme und Ausscheidung von Salizylamid bei oraler und perkutaner Anwendung.) EULER, E., and REMY, R. (1951). *Z. Rheumaforsch.*, **10**, 155. 25 refs.

The Serum Albumin Level in Acute Rheumatism in Childhood. (Über das Serumeiweissbild bei kindlichem akutem Gelenkrheumatismus.) KÖRVER, G. (1951). *Z. Rheumaforsch.*, **10**, 184. 3 figs.

The Prevention of Endocarditis in Rheumatic Fever. (La profilassi della endocardite nella malattia reumatica.) COCCHI, C. (1951). *Riv. Clin. pediat.*, **6**, 385.

Acute Rheumatism and Rheumatic Heart Disease. CONYBEARE, E. T. (1951). *J. roy. sanit. Inst.*, **71**, 300. 8 refs.

ACTH in the Treatment of Rheumatic Fever. (Behandling af febris rheumatica ned ACTH.) RØGEL, J. (1951). *Nord. Med.*, **45**, 806. 6 figs, 8 refs.

Acute Rheumatic Fever in the Young Adult White Male. HIRSCH, J. C., and FLETT, D. M. (1951). *Amer. J. med. Sci.*, **221**, 599. 4 figs, 43 refs.

Rheumatic Pericarditis in Early Childhood. FOX, E. G. (1951). *Brit. Heart J.*, **13**, 409. 4 refs.

The Role of Hypersensitivity in Rheumatic Fever. WEAVER, N. K. (1951). *Sth. med. J. Bgham, Ala*, **44**, 711. 7 figs, bibl.

Chronic Articular Rheumatism (Rheumatoid Arthritis)

Some Experiences in the Use of the Adrenaline Test in 51 Cases of Rheumatoid Arthritis. PARR, L. J. A., SHIPTON, E. A., and WHITE, P. (1951). *Med. J. Aust.*, **1**, 682. 23 refs.

Of 51 cases of rheumatoid arthritis tested, all but seven responded to 0·5 mg. adrenaline subcutaneously by a fall in eosinophil count of 50 per cent. or more; 23 out of 34 examined also showed a polymorphonuclear leucocytosis and a relative lymphopenia: thirteen had an initial lymphocytosis.

In view of the normal adrenocortical response to adrenaline in most cases of rheumatoid arthritis the authors used the drug therapeutically and claim that it "is productive of outstanding benefit in febrile rheumatoid arthritis and is often of great value in the chronic vasospastic varieties of the disease". In addition, their observation that lymphocytosis with lymphadenopathy commonly occurs in rheumatoid arthritis was used as the rationale for treating some cases by *x*-ray therapy to the thymus and mediastinum. The authors claim to have produced remissions thereby, with reduction in or return to normal of the erythrocyte sedimentation rate. A negative reaction to Thorn's test in rheumatoid arthritis is said to indicate the need for cortisone, and combinations of adrenaline and insulin are said to be more effective than adrenaline alone. Nevertheless, some cases appeared to have clinical remissions after adrenaline treatment in the absence of eosinopenia. This is accounted for by postulating the production of two separate hormones by the adrenaline-stimulated adrenal—one responsible for eosinopenia and the other for lymphopenia. Presumably either can induce a clinical remission.

It is concluded that most patients with rheumatoid arthritis have a normally reacting pituitary-adrenocortical mechanism, and that in many cases an overactive thymico-lymphatic system (as in the so-called "status thymico-lymphaticus") causes increased sensitivity to the bacterial and other antigens which the authors believe to be the cause of most cases of rheumatoid arthritis. Increased production of adrenal steroids is required to counter this sensitivity state, which may also be reduced by *x*-ray therapy.

[Few details of the case histories or of the dosage and total amounts of adrenaline used are given. No detailed criteria of "remission" are stated and no control experiments are mentioned. It appears that in addition to adrenaline many cases were also treated concurrently with benzyl sulphanilamide and large doses of ascorbic acid. The authors also claim good remissions from the use of benzyl sulphanilamide alone, and these are attributed to "suppression of bacterial antigens".]

Ellis Dresner.

A Contribution to the Pathology of Sjögren's Disease. ELLMAN, P., WEBER, F. P., and GOODIER, T. E. W. (1951). *Quart. J. Med.*, **20**, 33. 7 figs, 7 refs.

A case of Sjögren's disease lasting 8 years is described, which began in a woman of 35 with dryness of the mouth and painless parotid swellings, and ended with bronchopneumonia following a spontaneous pneumothorax. At necropsy, chronic inflammatory changes with degeneration and atrophy were found in the lacrimal, salivary, and mucus-secreting glands of the nasopharynx and respiratory and upper alimentary tracts, and in sweat glands of the skin. It is suggested that this inflammatory atrophy, of unknown causation, forms the pathological basis of the disease and that the resulting dryness leads to obstruction of the ducts, resulting in a secondary inflammatory granulomatous process and possibly suppuration.

[Professor Dorothy Russell's detailed description of the histological appearances in 36 slides gives additional value to this report.] *Ernest T. Ruston.*

A Case of Sjögren's Syndrome Treated with Adrenocorticotrophic Hormone. [In English.] FRENKEL, M., HELLINGA, G., and GROEN, J. (1951). *Acta endocrinol., Kbh.*, **6**, 161. 21 figs, 14 refs.

A case of Sjögren's syndrome is reported. The patient, a woman of 51, was given 50 mg. ACTH on the first day, then 30 to 40 mg. daily, the dosage being gradually reduced. Treatment was continued for 31 days. At the end of the first week of treatment the swelling of the parotid and lacrimal glands began to diminish, and in a fortnight had completely disappeared. After 3 weeks salivation returned, the lingual mucosa regenerated, and the tongue became completely normal in appearance. Lacrimal secretion also returned and the white filaments and erosions disappeared from the cornea. Fever subsided and there was marked euphoria. There was no joint involvement in this case even before treatment, except for occasional pain and crepitation in the knees. Improvement was maintained in spite of reduction in the dosage, but the parotid swelling and dryness of the mouth returned one month after treatment was discontinued.

During treatment the eosinophil count fell, neutrophil count rose, blood uric acid : creatinine ratio, and urinary 17-ketosteroid excretion rose, and the erythrocyte sedimentation rate fell. Detailed metabolic studies were carried out; there was retention of water and sodium, a fall in haemoglobin level, haematocrit reading, and serum protein level, slight hypochloraemia, and marked hypopotassaemia, the latter being accompanied by signs of over-action of the heart and the characteristic electrocardiographic changes.

Towards the end of treatment spasm of the central artery of the right retina developed, with loss of vision which had recovered only to the extent of light-perception at the time of the report. It was not clear whether or not this was the result of treatment with ACTH; the authors could trace no previous report of such a complication. *Robert de Mowbray.*

A Case of Sjögren's Disease with Scleroderma. HARRINGTON, A. B., and DEWAR, H. A. (1951). *Brit. med. J.*, **1**, 1302. 2 refs.

A man of 59 complained of dryness of mouth and eyes, and had a positive Schirmer's test. He had blepharitis but the corneae and lacrimal glands appeared normal; this was associated with dryness and thickening of the skin with pigmentation and loss of elastic tissue. The patient was not improved by vitamin A therapy.

P. L. Baxter.

Sjögren's Disease associated with a Pulmonary Lesion and Nephrocalcinosis. NELLEN, M. (1951). *S. Afr. med. J.*, **25**, 401 and 427. 4 figs, 31 refs.

After a comprehensive survey of the literature, taking into consideration the modern publications (Weber, Sheldon, and Raffle) which describe the numerous general and constitutional symptoms which might be found in Sjögren's disease, the author describes a case of his own. It concerns a woman aged 50 who, in addition to a marked dryness of the conjunctivae due to atrophy of the lacrimal glands, and superficial punctate keratitis, showed a bilateral calcification in the kidneys, giving an outline of the calyces. There were bronchopneumonic areas in the middle and lower zones of both lungs, with corresponding auscultatory signs. The

pathology of the different constitutional signs is discussed in some detail, and a probable explanation of their pathogenesis is given. *A. Jokl.*

Sjögren's Syndrome with Raynaud's Disease and Scleroderma. (Syndrome de Sjögren associé à une maladie de Raynaud et à une sclérodermie.) OURGAUD, A. G. (1950). *Bull. Soc. Ophtal. France*, No. 9, 816. Case report. *J. Rougier.*

The Agglutination of Sensitized Sheep's Erythrocytes by the Serum in Rheumatoid Arthritis. (Zur Agglutination sensibilisierter Hammelblutkörperchen durch Blutserum bei chronischer Polyarthritis.) TISCHENDORF, W., FRANK, A., and PUNIN, W. (1951). *Rheumaforsch.*, **10**, 189. 3 refs.

Rheumatoid Arthritis in the Aged. CECIL, R. L., and KAMMERER, W. H. (1951). *Amer. J. Med.*, **10**, 439. 4 refs.

Chronic Arthritis of Senescence. CECIL, R. L. (1951). *Geriatrics*, **6**, 179.

Parkinsonism and Rheumatoid Arthritis. WALLERSTEIN, R. O. (1951). *Ann. intern. Med.*, **34**, 899. 4 refs.

Rheumatoid Arthritis with Death from Medullary Compression. DAVIS, F. W., and MARKLEY, H. E. (1951). *Ann. intern. Med.*, **35**, 451. 14 refs.

Keratoconjunctivitis Sicca and Rheumatoid Arthritis. (Kerato-conjunctivitis sicca y artritis rheumatoidea.) LACKINGTON, C., CHARLIN, C., and GORMAZ, A. (1951). *Rev. méd. Chile*, **79**, 233. 1 fig., 9 refs.

Still's Syndrome in Juvenile Rheumatoid Arthritis. Its Clinical Aspects with a Review of the Literature on the Peculiarities of this Syndrome. SPODICK, D. H. (1951). *Arch. Pediat.*, **68**, 274. 32 refs.

The Morphology and Pathogenesis of Felty's Syndrome. (Über Morphologie und Pathogenese des Felty-Syndroms als Beitrag zum Problem des Rheumatismus.) PLIESS, G. (1951). *Frankfurt. Z. Path.*, **62**, 284. 4 figs, bibl.

The Therapeutic Response of Rheumatoid Arthritic Conditions to Intradermal Procaine and Adrenaline. COLLINS, P. A. (1951). *J. Irish med. Ass.*, **29**, 61. 1 ref.

The Effect of Transfusions of Pregnancy Blood in Rheumatoid Arthritis and Rheumatic Fever. (Influenza delle trasfusioni di sangue di donna gravida nella artrite reumatoide e nella febbre reumatica.) TOMMASO, L., and ANTONIO, P. (1951). *Policlinico* (*sez. med.*), **58**, 221. 5 figs, bibl.

Treatment of Rheumatoid Arthritis with Sodium cupro-alleje-thiourea benzoate. (Il trattamento del reumatismo articolare cronico con cupro-allyl-tiourea benzoato sodico.) MARIGO, S. (1951). *Minerva med., Torino*, **42**, 1169. 7 refs.

The Insulin Treatment of Rheumatoid Arthritis. (Die Insulinbehandlung der rheumatischen Arthritis.) KRESBACH, E., and STEPHANTSCHITZ, G. (1951). *Wien. klin. Wschr.*, **63**, 536. 2 figs, 20 refs.

Gold Therapy *versus* Hormone Therapy in the Treatmen. of Rheumatoid Arthritis. CECIL, R. L. (1951). *Intt rec. Med.*, **164**, 237.

Role of Penicillin in the Prophylaxis of Acute Rheumatoid Arthritis. (Le rôle de la pénicilline dans la prophylaxie du rhumatisme articulaire aigu.) RAVINA, A. (1951). *Pr. méd.*, **59**, 976. 2 refs.

Clinical and Biological Results of Different Forms of Treatment in Rheumatoid Arthritis. (Résultats cliniques et biologiques obtenus avec differents essais de traitement dans la polyarthrite chronique évolutive.) DE FOSSEY, B. M., COURJARET, J., and DELTOUR, G. (1951). *Pr. méd.*, **59**, 799. 4 figs, 13 refs.

The Treatment of the Exudative Manifestations of Rheumatoid Arthritis. (Zur Behandlung exsudativer Zustandsbilder der rheumatischen Infektarthritis.) WEITZMANN, G. (1951). *Münch. med. Wschr.*, **93**, 838. 20 refs.

Investigations on Specific Antibodies in the Plasma of Patients suffering from Cardio-articular Rheumatism or Rheumatoid Arthritis. ALES, J. M., ARJONA, E., JIMÉNEZ DÍAZ, C., LÓPEZ GARCÍA, E., MARTÍNEZ, J., and SEGOVIA, J. M. (1951). *Bull. Inst. med. Res., Madr.*, **4**, 89. 14 refs.

Researches on Hepatic Function in Rheumatoid Arthritis. (Richerche sulla funzionalità epatica nella poliartrite cronica primaria.) MANNETTI, C., and RIVANO, R. (1951). *Inform. med., Genova*, **5**, 136. Bibl.

Myocardial Infarction developing during Desoxycorticosterone Therapy for Arthritis. SILVERMAN, J. J., and SCHROEDER, C. T. H. (1951). *N.Y. St. J. Med.*, **51**, 1427. 1 fig., 11 refs.

Denervation of the Carotid Sinus in Six Cases of Rheumatoid Arthritis. (Six cas d'énervation sinusale pour polyarthrite chronique évolutive.) RENON, C., LE BIHAN, R., and MARTY, J. (1951). *Mem. Acad. Chir., Paris*, **77**, 396.

(Spondylitis)

Spondylitis Tuberculosa and its Relation to Neurological Affections. [In English.] DE VET, A. C. (1950). *Arch. chir. neerl.*, **2**, 303. 5 figs, 45 refs.

The author, at the Neurosurgical Clinic, Wassenaar, reviews 35 cases of tuberculous spondylitis. He points out that a neurosurgeon will see transverse cord lesions due to tuberculous vertebral disease quite often before a diagnosis of tuberculosis has been made, whereas the tuberculosis specialist watches the cord lesion develop in the patient already diagnosed as tuberculous. He quotes extensively from the work of others, notably Sorrel-Déjérine (*Contribution à l'étude des paraplégies Pottiques*, Paris, 1926).

He attempts to classify the stages of the illness and the need for operation thus: (1) Those cases of tuberculous

spondylitis developing a transverse lesion at an early stage while undergoing treatment usually undergo spontaneous cure and rarely require operation. (2) Those developing after a year of treatment may require operation. (3) Those where the diagnosis of tuberculous spondylitis is made when the patient is being examined for an initial neurological lesion should not be subjected to operation. (4) It is possible to find epidural tuberculosis without spondylitis.

The author warns against misdiagnosing these neurological lesions as due to disk herniation, for the result is likely to be fatal if the patient is subjected to operation. Tomography may be a valuable aid in diagnosis. If a decompression operation is undertaken it should be a ventral decompression according to the technique of Alexander and Dott. Laminectomy does not relieve pressure adequately; it merely weakens further the bony spinal column. Streptomycin is a valuable aid as a chemotherapeutic cover during operation.

Elliot E. Philipp.

Some Observations on 100 Cases of Ankylosing Spondylitis. PARR, L. J. A., WHITE, P., and SHIPTON, E. (1951). *Med. J. Aust.*, **1**, 544. 12 refs.

The authors studied 100 cases of ankylosing spondylitis from the eastern States of Australia. The ratio of males to females was 5 : 4, lower than that from seven English and American sources quoted. The average age at onset was 26 years. The disease was, on the average, milder in women than in men. Initial peripheral involvement was found in 6 per cent. of cases.

Associated factors such as the body build, climate, pre-existing tuberculous and gonococcal infections, and military service did not seem to be aetiologically important. Significant family history was elicited in 11 per cent. of cases.

Unlike rheumatoid arthritis, the ankylosing spondylitis manifested itself for the first time during pregnancy in five cases, and in a number of cases was aggravated by it. Iritis was recorded in 4 per cent. of cases. The erythrocyte sedimentation rate (E.S.R.) was raised in only 45 per cent. of cases; on the other hand, a number of symptom-free cases manifested a " much raised " E.S.R. for several years. [These findings contract with those of Simpson and Stevenson (*Brit. med. J.*, 1949, **1**, 214), who found a definite correlation between the rise in E.S.R. and the severity of the disease.] Changes in plasma proteins did not differ from those recorded by previous observers and were similar to the ones found in rheumatoid arthritis.

The importance is stressed of an early clinical diagnosis and of an immediate institution of *x*-ray treatment, before the appearance of unequivocal radiological signs, which may only appear some years (up to seven in the present series) after the onset of symptoms. Morning stiffness, which disappears with exercise, in a young subject should at once arouse suspicions. Good response to *x*-ray therapy confirms the diagnosis in doubtful cases. The correct diagnosis had been made in less than half the recorded cases before examination by the authors, who therefore advocate a routine *x*-ray examination of sacro-iliac joints in all young adults complaining of vague rheumatic pains anywhere in the body for a year or more. *X*-ray therapy was found valuable in all stages of the disease; in only 4 per cent. of the cases was there no improvement at all. Early treatment is urged, however, to prevent disability.

A. Swann.

Iritis associated with Spondylitis Ankylopoietica. [In Chinese.] CHAN, E., and SUN, S. F. (1951). *Nat. med. J. China*, **37**, 460. 5 refs.

Ankylosing Spondylitis associated with Sarcoidosis. (Association de spondylite ankylosante et de sarcoïdose.) VERSTRAETEN, J. M., and BEKAERT, J. (1951). *Acta tuberc. belg.*, **42**, 149. 2 figs, 10 refs.

Parathyroidectomy and Ankylosing Polyarthritis. (Parathyroidectomie et polyarthrite ankylosante.) PAOLUCCI DI VALMAGGIORE, R., and TOSSATI, G. (1951). *Pr. méd.*, **59**, 936. 7 figs.

Vertebral Rheumatism. (Reumatismos vertebrales.) BERTANI, G. C. (1951). *Prensa med. argent.*, **38**, 131. 2 figs.

Ankylosing Spondylarthritis. (Espondilo-artritis anquilosante.) LOSADA, M., and FRANCE, O. (1951). *Rev. argent. Reum.*, **16**, 2. 40 refs.

The Early Diagnosis of Spondylitis Ankylopoietica. (Zur Frühdiagnose der Spondylitis ankylopoetica.) MOHING, W. (1951). *Med. Klinik.*, **46**, 565.

(Miscellaneous)

The Use of Cholinergic Drugs in the Treatment of Muscle Spasm in Rheumatoid Arthritis. With special reference to Stigmonene Bromide. COHEN, A., and GOLDMAN, J. (1951). *J. Philad. gen. Hosp.*, **2**, 46. 1 fig., 7 refs.

Sodium Gentisate in Acute Articular Rheumatism. (Le gentisate de sodium dans le rhumatisme articulaire aigu.) GIRARD, M. (1951). *J. Méd. Lyon*, **32**, 231.

Clinical Experience with Crowe's Vaccine in the combined Management of Arthritis. PHILLIPS, K. (1951). *Sth. Med. Surg.*, **113**, 68. 4 refs.

Artificial Fever Therapy in Acute Articular Rheumatism resistant to Salicylates. (Pyretothérapie et rhumatisme articulaire aigu salicylo-resistant.) OURY, P., and FAYARD, F. (1951). *Rev. Rhum.*, **18**, 125.

The Sodium Salt of *alpha*-Glycerophospheric Acid in the Treatment of Chronic Joint Disease. (Il sale sodico dell'acido *alfa*-Glicerofosforico nella terapia delle artropatie croniche.) PRINCIPE, U. (1951). *Settim. med.*, **39**, 54. 22 refs.

Marisone in the Treatment of Arthritis. DURIVAGE, J. (1951). *Canad. med. Ass. J.*, **65**, 119.

Sun and Sand Baths in the Treatment of Chronic Non-tuberculous Arthritis. (I bagni di sole e di sabbia nel trattamento delle artriti croniche non tubercolari.) PALTRINIERI, M. (1951). *Minerva med., Torino*, **2**, 167.

Chronic Polyarthritis and Monarticular Trauma. KELLY, M. (1951). *Med. J. Aust.*, **2**, 197. 9 refs.

The Effect of Cortisone on the Course of Chronic Rheumatism. (Étude du comportement des rhumatismes chroniques soumis à la cortisone.) FORESTIER, J., CERTONCINY, A., JACQUELINE, F., and SAINT-MARC, J. (1951). *Rev. Rhum.*, **18**, 167.

Management of the Ambulant Arthritic Patient. PRUCE, A. M. (1951). *J. med. Ass. Ga*, **40**, 101.

The Ocular Complications of Arthritis. VAIL, D. (1951). *Sth. med. J. Bgham, Ala*, **44**, 317. 3 refs.

Sciatica

A Method of Measuring Reflex Times applied in Sciatica and other Conditions due to Nerve-root Compression. MALCOLM, D. S. (1951). *J. Neurol. Psychiat.*, **14**, 15. 8 figs, 11 refs.

The author has devised a technique for measuring the reflex time of the ankle-jerk and the knee-jerk and finds that this time is constant in normal adults. When examining patients with compression of one nerve root by a protruded intervertebral disk, he found that with unilateral lesions there was a delay of 1 to 4 milliseconds in five out of seven cases as compared with the normal side, while in the remaining two cases there was no difference between the two sides. To find out at what level this delay occurred he measured, at operation, the conduction time in the motor root past the compressed segment of the nerve and compared this with the conduction time in the corresponding root on the opposite side, and in five out of seven cases there was a delay of 1 to 6·5 milliseconds; in the remaining two cases, where there was bilateral compression, no difference could be detected between the two sides. He concludes that the increased reflex time is due to delayed conduction through the compressed segment of the nerve. Clinical assessment of a diminished tendon reflex does not always run *pari passu* with a delay in conduction time.

J. W. Aldren Turner.

Results of Surgery in Sciatica and Low Back Pain. BURNS, B. H., and YOUNG, R. H. (1951). *Lancet*, **1**, 245. 7 refs.

A disk lesion is the commonest cause of lumbago and sciatica, and diagnosis is seldom difficult. Only about one in forty of these patients need operation; in the others the attack is brief and is alleviated by rest in bed or by a plaster jacket and local heat. Manipulation is rarely successful and may make the patient worse; routine physiotherapy also appears valueless. Operation is indicated in: (1) patients with severe pain not improving after 3 weeks' rest in bed; (2) patients with repeated attacks; and (3) patients with chronic "lame backs" preventing them from working. This group usually requires spinal fusion. Laminectomy is performed in the lateral position, and both the fourth and fifth lumbar disks are explored.

The authors have operated on 913 patients between 1940 and 1948; the findings were: protrusion, 750; lesions without a protrusion, 82; osteo-arthritis causing root irritation, 22; abscess, 3; tumour, 2; peridural adhesions, 12; and negative, 42.

Protrusions were of two types, the nuclear protrusion and the annular tear, although the commonest lesion was a combination of the two. Lesions without a protrusion were either a bulging annulus with degenerated nucleus, a soft spot (Dandy's concealed disk), or a scarred disk with an adherent nerve root. The prominence of the signs and symptoms is normally directly related to the size of the disk protrusion, and lesions without protrusion of the disk are usually seen in patients operated upon between attacks or in cases of chronic backache. Sciatic scoliosis is nearly always associated with a protrusion of the disk between L4 and L5; with this exception, location by physical signs is unreliable. Protrusions of the 2nd and 3rd lumbar disks give rise to irritation of the femoral nerve and a positive femoral-stretch sign. Midline protrusions cause only backache unless very large, when they may give rise to bilateral sciatica. Where no disk lesion is found on exploration, attacks of pain usually continue and it is assumed that a protrusion, which may have returned at the time of operation, has been missed. Of the 750 found to have a protrusion at operation 616 were followed up. The results were: no pain or disability, 349 (56·6 per cent.); occasional pain, 98 (15·9 per cent.); improved, 125 (20·3 per cent.; and failures, 44 (7·2 per cent.).

Age appears to have no effect upon the prognosis, nor does the duration of symptoms before operation. A total of 133 patients were symptom-free on discharge from hospital, but subsequently developed pain; this was often an isolated attack, but in eighteen a further exploration was necessary and in each a further prolapse was found, most commonly of another disk. In 22 out of 44 patients who had continuous pain after the first operation further exploration was carried out; nine of these had another protrusion, six another disk, emphasizing the importance of inspecting both disks even when a lesion has been satisfactorily demonstrated at one level; the remaining thirteen showed dense adhesions, either associated with infection or as a reaction to glove powder. The results in cases of a lesion without a protrusion are less good. In patients with low-back pain alone, relief is obtained if there is a marked protrusion; when a softened disc only is present, fusion gives better results.

Spinal fusion is indicated in spondylolisthesis, adhesions following removal of a prolapsed disk, and certain cases of backache where the signs are minimal, indicating that there is no disk protrusion. Fusion has been performed with two tibial grafts to the spinous processes and, latterly, iliac grafts to the laminae. More recently the grafts have been bolted in position, with a spring washer to maintain compression, and this had led to a more rapid and certain fusion. Of 82 cases in which grafting was used, definite fusion was obtained in only 37, but where solid fusion was achieved symptoms were nearly always relieved.

Peter Ring.

The Treatment of Lumbago and Sciatica by Manipulation. (Le traitement des lombalgies et des sciatiques par les manipulations.) LIÈVRE, J. A., ATTALI, P., and LECA, A. (1951). *Pr. méd.*, **59**, 850. 12 refs.

The Treatment of Sciatica with Glucurone. HODAS, J. H., LAAGE, H., and BRANDON, H. (1951). *N.Y. St. J. Med.*, **51**, 1171. 8 refs.

The Problem of the Common Case of Low Back Pain. MENNELL, J. McM. (1951). *Stanford med. Bull.*, **9**, 88.

Backache, Sciatica, and Ruptured Discs. PRIDIE, K. (1951). *Bristol med.-chir. J.*, **68**, 95.

Gout

The Syndrome of Gout. MCQUEEN, E. G. (1951.) *Med. J. Aust.*, **1**, 644. 49 refs.

The Problem of Gout. DILLINGER, G. R. (1951). *J. med. Ass. Ga*, **40**, 114. 9 refs.

Early Diagnosis and Management of Gout. SUTTENFIELD, F. D. (1951). *Geriatrics*, **6**, 96. 11 refs.

The Therapeutic Action of ACTH and Cortisone in Gout. (Action thérapeutique de l'ACTH et de la cortisone dans la goutte.) COSTE, F., GLAMICHE, P., and PIQUET, B. (1951). *Rev. Rhum.*, **18**, 215. 10 refs.

Non-Articular Rheumatism

Subcutaneous Rupture of the Tendo Achillis. BATE, T. H. (1951). *Arch. Surg., Chicago*, **62**, 14. 23 refs.

This paper deals with subcutaneous rupture of the tendo Achillis, a rare accident. The author has reviewed the literature on this subject and has found that the condition can be classified as due to: (1) pathological subcutaneous rupture; or (2) traumatic subcutaneous rupture. The former is associated with minimal trauma, which is superimposed upon some disease such as syphilis or ossification of the tendo Achillis. These cases are proved by *x*-ray examination and at operation.

Traumatic subcutaneous rupture of the tendo Achillis may result from: (1) direct trauma at the site of rupture of the tendon without dissolution of continuity of the skin; or (2) sudden contracture of the gastrocnemius and the soleus muscles. This occurs most commonly at the start of a step, when the ball of the foot leaves the ground and when the weight of the body has to be received by the ankle-joint on the strongly bent knee, or at the moment of leaping down. Thus violent stretching of the actively contracted muscle occurs and the less elastic tendon may split.

The pathological anatomy is discussed and it is stated that the rupture may be complete or incomplete. The former is the more frequent occurrence seen at operation. In the case of a pathological rupture there is little pain at the time of the accident. Walking is usually painless and so is palpation, although palpation shows a depression. With traumatic rupture pain is an invariable symptom. The patient not only feels the pain but frequently hears the rupture; he cannot rise on his toes and he limps. Ecchymosis is frequent. The diagnosis is not difficult and the author includes tenocellulitis and retrocalcanean bursitis and traumatic tendinitis Achillis in the differential diagnosis. *X*-ray examination is useful. The prognosis in untreated cases from the functional point of view is not good, there being difficulty in standing on the toes, oedema, persistent pain, limping, and frequent falls. Incomplete rupture has a worse prognosis than complete.

Treatment may be either conservative or operative. Operative treatment in which the tendon is sutured is the method of choice. A few patients walk after 20 days, and return to work in the first month or two. In contrast, with conservative treatment much time is required before the patient is able to resume walking.

The author reports two cases of this rare condition.

Leon Gillis.

Lesions of the Musculotendinous Cuff of the Shoulder. IV. Some Observations Based upon the Results of Surgical Repair. MCLAUGHLIN, H. L., and ASHERMAN, E. G. (1951). *J. Bone Jt Surg.*, **33A**, 76. 14 refs.

For repair of a ruptured tendon cuff the acromion is divided transversely and the outer part discarded, the tendinous part of the deltoid being united at the end of the operation with the tissues over the acromial stump. Except in the very thin patient no visible defect occurs, and function is unimpaired. Removal of calcified deposits in the tendons is performed through a short deltoid-splitting incision.

Patients with complete cuff tears are unable to initiate abduction or to maintain the arm in an abducted position against gravity, but when the tear is less than 3 cm., elevation is not lost even though the lesion extend across the whole of the supraspinatus tendon. Most ruptures are due to minor trauma to degenerated tendon tissue, and symptoms are often present before the injury. Signs of importance in diagnosis include absence of restriction of passive movement and atrophy of the spinati muscles with hypertrophy of the deltoid. Operation is felt to be indicated only in patients with extensive damage and those with persistent symptoms. Most patients improve on conservative treatment, with rest in a sling and physiotherapy as the pain diminishes.

Peter Ring.

Pathology of Calcareous Tendinitis and Subdeltoid Bursitis. PEDERSEN, H. E., and KEY, J. A. (1951). *Arch. Surg., Chicago*, **62**, 50. 9 figs, 7 refs.

This paper describes the gross and microscopical appearance of the lesions found in the rotator cuff of the shoulder in subdeltoid bursitis with calcification. Codman believed that the inflammation was caused by the presence of degenerated material in the tendon and later in the bursa, the bursitis being secondary to the degeneration of the tendon. He noted inflammatory changes in the tendon without the presence of demonstrable calcium in the radiograph, and stated that this might produce symptoms similar to those present in subdeltoid bursitis with calcification.

The present authors' observations are based on the examination of material removed at operation on 55 patients for subdeltoid bursitis with calcification. This showed that the basic process is one of degeneration of tendon or muscle in the rotator cuff of the shoulder. Calcium is deposited in the necrotic tissues. When there are large collections of necrotic calcified material they are enclosed by a granulomatous wall and may be seen on *x*-ray examination. The inflammation and the tissue tension produce pain, although this may also be mechanical. But the primary cause is the large calcified necrotic focus which is seen on *x*-ray examination, and the most effective treatment is the evacuation of the focus. These lesions are associated with capsular contracture and fibrous adhesions in the intertubercular sulcus, and treatment should be directed to the entire shoulder joint.

Leon Gillis.

The Frequency of Fatty Herniae with Necrotic Lesions as a Cause of Lumbago. (La frecuencia de hernias grasas con lesions necróticas como causa de lumbago.) DAL LAGO, H., and VERA, R. A. (1950). *Rev. Ortop. Traum.*, **20**, 160. 4 figs.

The authors state that fatty herniae are a common cause of lumbago in the lumbosacral and iliac regions. 25 per cent. of these herniae show on operation necrotic lesions of a pseudo-cystic nature surrounded by areas of oedema. Four good photographs illustrate the paper, which is a preliminary communication only.

René Mendez.

Myalgia Epidemica or Bornholm Disease. (Myalgia epidemica čili bornholmská nemoc.) POPEK, K., and NOSOVÁ, T. (1951). *Lék. Listy*, **6**, 313. 34 refs.

ACTH, Cortisone, and other Steroids

Observations during ACTH and Cortisone Administration to a Patient with Longstanding Panhypopituitarism and Rheumatoid Arthritis. SCHROCK, C. E., SHEETS, R. F., and BEAN, W. B. (1951). *J. clin. Invest.*, **30**, 174. 4 figs, 16 refs.

A woman aged 46 developed hypopituitarism after the birth of her only child and subsequently became crippled with rheumatoid arthritis. Her arthritis improved when she was given cortisone, but not when she was given ACTH. A metabolic study showed that the adrenal gland was responding only incompletely to the stimulus of the ACTH. *H. V. Morgan.*

The Natural Course of Rheumatoid Arthritis and the Changes Induced by ACTH. GIANSIRACUSA, J. E., ROPES, M. W., KULKA, J. P., and BAUER, W. (1951). *Amer. J. Med.*, **10**, 419. 11 figs, 10 refs.

The authors report observations made on a young woman treated for rheumatoid arthritis at the Massachusetts General Hospital, Boston, between 1942 and 1949. This 7-year period included an initial phase of active disease, a spontaneous remission, a post-operative exacerbation, an ACTH-induced remission, and two ACTH-withdrawal exacerbations. The clinical, radiological, and laboratory findings are described in detail for each stage of the disease.

ACTH was given initially in doses of 100 mg. daily. A mild exacerbation occurred on the 65th day of treatment, when the dose of ACTH had been reduced to 42 mg. per day, but a further remission occurred on increasing the dose. A severe psychosis which developed on the 130th day necessitated the withdrawal of ACTH. Objective signs of an exacerbation developed on the 12th post-ACTH day, and the signs approximated to the pre-ACTH level on the 19th day. The clinical changes observed during the ACTH-induced remission followed the usual pattern and were comparable to those seen during the spontaneous remission except that they occurred in weeks instead of many months. Hyperhidrosis of hands and feet and minor generalized lymphadenopathy were not influenced by ACTH administration. When the disease was active the following changes were noted in the serum protein fractions as determined electrophoretically: an increase in α-1, α-2, and gamma globulin and fibrinogen fractions and a marked reduction in the albumin fraction. The protein fractions changed in the direction of normal during the spontaneous and ACTH-induced remissions.

Synovial-fluid changes were followed during ACTH therapy, but observations made on the fluid during the spontaneous remission were not complete enough for a comparison to be made. The abnormalities in the fluid—namely, in the nucleated cell counts, the character of mucin, and the serum-fluid glucose difference—returned to normal after ACTH administration, but the viscosity increased to a point far beyond that for normal synovial fluid.

Observations made on the eosinophil counts, 17-ketosteroid excretion, and 11-oxycorticosteroid excretion during ACTH therapy followed the usual pattern. The effect of ACTH on liver function tests was also studied. The cephalin-flocculation and bromsulphalein reactions, which had previously been normal, became abnormal in the latter part of the ACTH period. The cholesterol-ester-cholesterol ratio decreased from 60 to 28 per cent. in the ACTH period, but whether this was due to increased adrenocortical activity or to impairment of liver function is not clear.

After 2 to 3 weeks of ACTH therapy a " moon facies " and other side-effects developed. Post-prandial hyperglycaemia, slight glycosuria, and moderate insulin resistance developed during the ACTH period. Observations were made on the serum electrolytes during ACTH therapy. The authors show that, although potassium deficiency was present when the patient became psychotic, this did not in fact contribute to the psychosis. There was no change in serum calcium or phosphorus levels until the 130th day of ACTH, when concurrently with the psychosis they rose to abnormal values (12 and 5 mg. respectively). Synovial tissue examined microscopically towards the end of the period of natural remission and after 110 days of ACTH revealed persistence of mild synovitis. *C. E. Quin.*

Evaluation of Steroids in Rheumatoid Arthritis. NORCROSS, B. M., LOCKIE, L. M., and TALBOTT, J. H. (1951). *N.Y. St. J. Med.*, **51**, 1031. 44 refs.

Testosterone, deoxycortone acetate (DCA) and ascorbic acid, 21-acetoxy Δ-5-pregnenolone, Δ-5-pregnenolone, 16-dehydro-pregnenolone, and cortisone were given to 67 patients; of these, 55 had rheumatoid arthritis, four rheumatoid arthritis associated with psoriasis, seven " rheumatoid spondylitis ", and one advanced osteoarthritis.

Testosterone was given intramuscularly to one female and seventeen male patients in a dosage of 150 to 300 mg. daily to a total of 3,000 to 4,500 mg. Eight of them were improved; most patients showed some gain in weight, in two oedema developed, and the female patient noticed hirsutes and deepening of the voice. DCA and ascorbic acid, in doses of 5 mg. intramuscularly and 1,000 mg. intravenously, respectively, was given daily to 23 patients. Seven showed slight improvement and three definite objective improvement. Erythrocyte sedimentation rates and eosinophil counts were unaltered. 21-Acetoxy-Δ-5-pregnenolone, in doses of 300 to 500 mg. intramuscularly daily for periods of 10 to 40 days, was given to thirteen patients. Two of these improved significantly; in the others there was no change in erythrocyte sedimentation rate, blood pressure, or biochemical values. Δ-5-pregnenolone, in doses of 400 to 500 mg. daily by mouth for 4 to 16 weeks, was given to 24

patients: only two responded. 16-Dehydro-pregnenolone, 100 mg. daily intramuscularly, was given to seven patients: two showed slight improvement; in five patients multiple abscesses developed.

Cortisone was given to 24 patients, of whom 22 had received at least one previous course of steroid therapy without improvement. All responded well, with lowering of the erythrocyte sedimentation rate and an initial eosinopenia. Euphoria was noted in eighteen patients.

One patient, who had Addison's disease in addition to rheumatoid arthritis, developed a complete remission of the arthritis and improvement in the symptoms of Addison's disease on an initial dose of 25 mg. Cortisone in a daily dose of 12·5 mg. maintained this remission.

B. E. W. Mace.

Effects of Pituitary Adrenocorticotropic Hormone (ACTH) in Rheumatoid Arthritis. MARGOLIS, H. M., and CAPLAN, P. S. (1951). *J. Amer. med. Ass.*, **145**, 382. 3 figs, 12 refs.

Short-term administration of ACTH in rheumatoid arthritis is almost invariably followed by relapse when the hormone is withheld. The authors decided to study the effects of long-term administration of this substance and to investigate the safety of such long-term administration and the means by which the remission, once induced, might be maintained. As gold is known to induce remission in certain cases, they studied the possibility of combining hormone therapy with subsequent chrysotherapy to maintain the remission.

The group which they studied totalled 56 patients; 46 of these were treated for periods from 2 to 7 months, the remainder for shorter periods: 23 patients were treated with gold and ACTH; 33 with ACTH alone. Tables are given to show the duration of disease, varieties of associated organic disease, age distribution, and dosage of ACTH employed.

Of the 56 patients, forty responded satisfactorily to treatment with ACTH, twelve showed some improvement, and four did not respond. Of these last, one had very severe arthritis with ankylosis of many joints and three had severe psychoneurotic symptoms. Of the patients who responded satisfactorily, the degree of response depended on the degree of structural change which was present before treatment started, but the response to a first course of injections was not necessarily reproduced by subsequent treatment. Similarly, long-continued therapy was not necessarily accompanied by continued satisfactory response, and some patients deteriorated during such treatment. However, seven patients who had responded satisfactorily remained in absolute remission for periods varying from 30 to 229 days after injections of ACTH had been withheld. All these seven patients had been treated with gold as well as ACTH. In discussing the combination of chrysotherapy and hormone therapy the authors point out that their figures suggest that this combination may possibly be of greater value than hormone injection alone and may prolong the effect of hormone therapy.

The laboratory investigations which were made revealed the fall in number of circulating eosinophils when ACTH was administered, but the degree of fall could not be correlated with the degree of improvement which occurred. In most patients there was a prompt rise in haemoglobin level and fall in the erythrocyte sedimentation rate. The sedimentation rate was apt to rise again when the amount of hormone administered was decreased or administration stopped. Half the patients developed side-effects and in most instances they were trivial; but they note that hypertension, hyperglycaemia with glycosuria, osteoporosis, mental depression, and cerebral confusion did develop in certain cases.

The authors conclude that ACTH has now a definite place in the therapeutic armamentarium. They suggest from their experience that it will prove most beneficial in the early case and that serious side-effects are infrequent. They stress their finding that long-continued administration is followed by a falling-off in the degree of response and by an increased tendency to the development of side-effects. Stresses and strains decrease the improvement obtained with ACTH and increase the liability to relapse. They feel that further investigation should be made into the value of combined chrysotherapy and hormone treatment and finally conclude that measures such as physiotherapy have by no means lost their value now that these new, potent preparations have arrived.

W. Tegner.

The Effect of ACTH on Psoriasis Arthropathica et Ungium. (Zur Wirkung des ACTH (Cortiphysob) auf die Psoriasis arthropathica et ungium.) KALKOFF, K. W. (1951). *Derm. Wschr.*, **123**, 361. 4 figs, 12 refs.

After a short review of the literature the author presents two cases of psoriasis arthropatica et ungium. The first patient gave a history of psoriasis for 23 years with involvement of the joints for 9 years and of the nails for one year; 67·5 mg. ACTH was given, with immediate improvement, and followed on the 22nd to 24th day by 90, 90, and 22·5 mg. ACTH respectively. All lesions responded well, but a recurrence of the skin and joint lesions occurred 8 months later. The latter in this case were acute, with periarticular oedema. The second patient had a similar history. She was given a course of ACTH (22·5 mg. 6-hourly, total 382 mg.) with a good clinical response, and 12 days later another course (90 mg. daily for 3 days, and then 22·5 mg. daily for 7 days). The skin lesions on the trunk healed, those on the arms improved, and no change was noted on the legs. This might be due to stasis in the thighs. The joint lesions, which were painless and chronic, remained unchanged.

In both cases the nails were cured and a distinct hyperkeratotic line of demarcation of several millimetres' breadth divided the affected, discoloured, distal part of the nail from the healthy, recently grown, proximal part. This line of demarcation indicated the time at which the ACTH took effect. By measurement of the distance between this line and the eponychium this time could be calculated with a moderate degree of accuracy, showing that the effect of ACTH is much more instantaneous than that of other methods of treatment, where the transition from affected to healthy nail can hardly be demonstrated at all.

Ferdinand Hillman.

Two Cases of Rheumatic Iridocyclitis treated with Cortisone Drops. (Tratamiento de dos casos de iridociclitis reumática por la cortisona.) BERNASCONI CRÁMER, E., IRIBARREN, R., CATOGGIO, J. P., and BUITRON, P. (1951). *Arch. Oftal. B. Aires*, **26**, 102. 19 refs.

Cortisone Therapy in Acute Rheumatic Carditis: Preliminary Observations. HARRIS, T. N., ABRAMS, W. B., LEO, T. F. P., and HUBBARD, J. P. (1951). *Circulation*, **3**, 215. 3 figs, 10 refs.

The authors have studied the effects of cortisone therapy in four cases of acute rheumatic carditis at the Children's Hospital and General Hospital, Philadelphia. The ages of the patients were 4, 13, 14, and 22 years. The daily dosage of cortisone was 112·5 mg., except for the 4-year-old child, who received 75 mg. daily. The 4-year-old received one course of treatment, the other patients two courses, the duration of a course being about 3 weeks.

Fever subsided in from 1 to 7 days from the beginning of cortisone therapy, except in one case in which the temperature fell slowly during the first course. Joint pains, where present, disappeared within 4 days. In three patients congestive cardiac failure developed 4, 10, and 20 days respectively after starting cortisone therapy; this responded well to the usual therapeutic measures while hormone therapy was continued. All cardiac murmurs present at the beginning of treatment were present at the end, and in addition three patients developed new murmurs. One patient developed *x*-ray evidence of cardiac enlargement while under treatment, but three patients with initial cardiac enlargement showed no change in this respect.

In one case electrocardiographic abnormalities—elevation of ST segment and inversion of T waves—disappeared during treatment, but inverted T waves returned in the chest leads when cortisone was finally discontinued. In another case there was a prolonged P-R interval which became normal during cortisone treatment, but at the same time the ST segment became progressively elevated as pericarditis developed. The erythrocyte sedimentation rate fell during treatment and only failed to return to normal in one case.

After cessation of the course of cortisone treatment, recrudescence of rheumatic activity occurred in all four patients. *C. E. Quin.*

Trial of a Cinchoninic Acid Derivative in some Collagen Diseases. RENNIE, J. B., MILNE, J. A., and SOMMERVILLE, J. (1951). *Brit. med. J.*, **1**, 383. 6 figs, 7 refs.

This report from The Western Infirmary, Glasgow, describes the effect of 3-hydroxy-2-phenylcinchoninic acid (HPC) in twelve cases of collagen disease. The oral dosage varied from 20 to 40 mg. per kg. body weight for 1 to 3 weeks. Fever and painful joints were relieved in four cases of rheumatic fever, and joint swelling rapidly disappeared in two out of three cases. A rapid partial fall in the erythrocyte sedimentation rate coincided with treatment in two cases. Heart size, quality of sounds and murmurs, and subcutaneous nodules were uninfluenced. Two patients relapsed following withdrawal of HPC. In one out of two patients with polyarteritis nodosa, HPC appeared to shorten the illness. The raised blood pressure fell to normal, fever, tachycardia, and alimentary symptoms disappeared, while fundal lesions regressed. Slight albuminuria and haematuria persisted. Striking clinical and histological improvement occurred in three patients with scleroderma, but two patients relapsed later.

Skin lesions in three cases of lupus erythematosus were thought to be less florid during HPC treatment, but this was not confirmed histologically. Toxic effects, which were infrequent, consisted of slight nausea, diarrhoea, and (rarely) vomiting. *I. Ansell.*

ACTH and Cortisone in Diffuse Collagen Disease and Chronic Dermatoses. Differential Therapeutic Effects. IRONS, E. N., AYER, J. P., BROWN, R. G., and ARMSTRONG, S. H. (1951). *J. Amer. med. Ass.*, 145, 861. 5 figs, 21 refs.

In the course of investigation and treatment of thirteen patients it was observed that some affections not responsive to cortisone, such as psoriasis, exfoliative dermatitis, and sclerœdema, were responsive to ACTH. In the collagenous diseases such as lupus erythematosus ACTH produced remissions more quickly than cortisone, but there was a high incidence of complications on long-term therapy. It was advantageous to start treatment with ACTH and then to substitute cortisone therapy. A salt-restricted diet and the administration of potassium were regarded as necessary, and the use of mercurial diuretics in patients with salt and water retention is discussed.

Permanent cure was not obtained in any of the cases treated, and one patient died. It is stressed that in cases where bacterial allergy may be an aetiological factor, treatment with antibiotics should be tried before employing ACTH or cortisone. There was not always a correlation between eosinophil response and clinical response to treatment. *John T. Ingram.*

The Effect of ACTH, Cortisone, and DCA with Ascorbic Acid on "Formalin-arthritis". PARKES, M. W., and WRIGLEY, F. (1951). *Brit. med. J.*, **1**, 670. 7 figs, 7 refs.

It was asserted by Selye in 1949 that adrenocorticotrophin (ACTH) and cortisone would prevent the acute and chronic stages of experimental "formalin arthritis", having in this respect an opposite type of action to deoxycortone acetate (DCA) which exacerbated this condition. He also asserted that the lesions of "formalin arthritis" microscopically resembled the rheumatic-fever lesion in the acute stage, and the rheumatoid lesion in the chronic stage.

The authors of this paper record their experience with "formalin arthritis" in the rat, employing an ingenious method of their own devising for evaluating changes in limb volume. Their results do not confirm Selye's statement that a "self-maintaining chronic inflammatory process" develops in the ankle-joint, showing "little or no sign of regression for weeks after the last injection". They frequently found that the limbs of their rats had returned to normal, or nearly so, by the end of 4 weeks, although histological examination did usually reveal some residual abnormality. Their observations also did not support the claim that DCA and ascorbic acid can prevent the development of "formalin arthritis"; indeed, in every case this combination exacerbated the acute oedematous response of the foot, which they also observed in animals treated with DCA alone. Neither cortisone nor ACTH had any effect on the swelling of the foot, nor did they appear to exert any protective action against "formalin arthritis".

As a result of their experiments, which are described in detail, they conclude that "formalin arthritis" in rats is unsuitable as a screening test for substances proposed for the treatment of the rheumatic diseases. *W. S. C. Copeman.*

3-0-Toloxy 1,2-Propanediol in the Treatment of Rheumatic Diseases. HERMANN, I. F., and SMITH, R. T. (1951). *J. Lancet*, **81**, 271. 8 refs.

Desoxycorticosterone Acetate and Ascorbic Acid in the Treatment of Rheumatoid Arthritis. LITTMAN, D. S., STOCKDALE, R. H., and WILLIAMSON, G. R. (1951). *Arch. intern. Med.*, **87**, 707. 5 figs, 6 refs.

Cortisone and ACTH in Rheumatology: Results of Treatment in 58 Cases. (Cortisone et ACTH en rhumatologie: resultats du traitement d'apres 58 observations.) DE SÈZE, S., ROBIN, J., ORDONNEAU, P., RYCKEWAERT, A., CAYLA, J., POINSARD, G., RIBIÈRE, M., CLÉMENT, D., and DEBEYRE, N. (1951). *Rev. Rhum.*, **18**, 177.

The Contraindications to Cortisone and ACTH in Inflammatory Rheumatism. (Quelques precisions sur les contres-indications de la cortisone et de l'ACTH dans les rhumatismes inflammatoires.) FORESTIER, J., CERTONCINY, A., and JACQUELINE, F. (1951). *Rev. Rhum.*, **18**, 184. 2 figs.

Rheumatoid Scleral Nodules (Scleromalacia Perforans) treated with Cortisone. TALKOV, R. H., COLPOYS, F. L., DAVIS, R. K., PAPPER, S., and FEINBERG, R. (1951). *Arch. intern. Med.*, **87**, 879. 6 figs, 19 refs.

Cortisone and ACTH in the Treatment of Rheumatic Conditions. (La cortisone et l'ACTH dans le traitement des maladies rhumatismales.) GAUCHER, M. (1951). *Gaz. méd. France*, **58**, 431.

A Clinical Contribution to the Treatment of Rheumatic Disease with Adrenal Cortical Extract associated with Ascorbic Acid. (Contributo clinico alla nuova terapia delle malattie reumatiche con estratti totali di corteccia surrenale associati a vitamina C.) BASSI, D., and ZOTTI, G. (1951). *Settim. med.*, **39**, 162. 32 refs.

The Biological Control of the Effects of ACTH and Cortisone in Rheumatoid Arthritis and Gout. (Controle biologique des actions de l'ACTH et de la cortisone dans la polyarthrite chronique évolutive et dans la goutte.) TRAVERSE, P. M. DE, and GERBAY, F. (1951). *Rhumatologie*, **3**, 107. 1 ref.

The Respective Characteristics of and Indications for Cortisone and ACTH in Rheumatic Conditions. (Caractères respectifs et indications de la cortisone et de l'ACTH dans les affections rhumatismales.) FORESTIER, J. (1951). *Rhumatologie*, **3**, 85.

Cortisone and ACTH in Rheumatology. Experience with 112 Cases. (Indications, résultats, accidents de la cortisone et de l'ACTH en rhumatologie d'après une expérience portant sur 112 cas.) DE SÈZE, S., ROBIN, J., RYCKEWAERT, A., ORDONNEAU, P., CLÉMENT, D., RIBIÈRE, M., DEBEYRE, N., and CARLIER, J. C. (1951). *Sem. Hôp. Paris*, **27**, 2354.

Deleterious Effect of Pregnenolone in Rheumatoid Arthritis. (Efecto paradojal de la pregnenolona en la artritis rheumatoidea.) SCHAPOSNIK, F., and GUTIÉRREZ, A. (1951). *Prensa med. argent.*, **38**, 1582. 2 figs, 10 refs.

Pituitary Implants in the Treatment of Rheumatism. (Implantace hypofysy v léčbě reumatismu.) HERMAN, B., and VYKYDAL, M. (1951). *Čas. Lék. čes.*, **90**, 829. 18 refs.

Effect of Cortisone and ACTH on the Histopathology of Rheumatic Carditis. Report of a Necropsied Case. SPAIN, D. M., and ROTH, D. (1951). *Amer. J. Med.*, **11**, 128. 4 figs.

21-Acetoxypregnenolone in the Treatment of Rheumatoid Arthritis. DAVIS, J. S., and BARTFIELD, H. (1951). *N.Y. St. J. Med.*, **51**, 1832. 4 refs.

Clinical Results of Cortisone and ACTH in Acute Rheumatic Carditis. A Case Study. TYSON, R. G. (1951). *Permanente Fdn med. Bull.*, **9**, 81. 1 fig., 14 refs.

Chorea Gravis (Sydenham's Chorea) treated with Cortisone and Ascorbic Acid. SCHWARZ, H. (1951). *Canad. med. Ass. J.*, **65**, 150. 4 refs.

Adrenocorticotrophin (ACTH) in the Treatment of Joint Disease. (L'ACTH nella terapia delle artropatie.) MORELLI, A., and DI BOSCO, M. M. (1951). *Rif. med.*, **65**, 281. 36 refs.

The Postoperative Use of Adrenal Cortical Extract. KELSO, J. W., and KEATY, C. (1951). *Surg. Gynec. Obstet.*, **92**, 296. Bibl.

Results of Cortisone Treatment in Dublin. MEDICAL RESEARCH COUNCIL OF IRELAND (1951). *Irish J. med. Sci.*, **6**, 95.

In this preliminary report on the clinical investigation of cortisone by the Medical Research Council of Ireland, fifteen cases of rheumatoid arthritis are described. The usual intramuscular dose of cortisone was about 100 mg., although double this dosage was often employed for a few days. The maximum degree of remission occurred in 2 to 6 weeks. A course at full dosage lasted 3 to 6 weeks and the total dosage did not exceed 6 g. A difficulty was to know how to treat cases which relapsed in a week or two after a full course, and required the hormone for long periods two to four times a week to keep the arthritis under control, especially when side-effects appeared. The best results were obtained in those cases treated before destructive lesions in the joints were sufficient to cause extensive damage to cartilage or bone. The estimation of functional improvement varied from between 70 to 85 per cent. In all cases, however, relapse was expected sooner or later and then cortisone treatment was to be resumed.

For ophthalmic work subconjunctival injection was decided upon as the method most likely to give maximum local concentration with the least danger of causing any general upset. A dose of 0·05 ml., containing 1·25 mg. cortisone, was given subconjunctivally under surface analgesia produced by 2 per cent. cocaine. There was little irritation. The material remained visible as a gradually decreasing deposit for 5 or 6 days, at the end of which time a second injection was given. Five types of case were considered suitable for cortisone therapy. In the first group of ocular complications of rheumatoid arthritis certain cases treated by the authors

cleared with rapidity. The second group, of conditions of the anterior segment in which bacteria were not the cause, such as interstitial keratitis, responded very satisfactorily. Other types of keratitis improved in about 60 per cent. of cases. In three cases of iridocyclitis there was some improvement. In the third group, consisting of healing corneal inflammations or burns (three cases of severe corneal opacities following lime and acid burns), clearing of the corneal opacity was accelerated and increased. In the fourth group no improvement was recorded in one case of vascular degeneration of the posterior segment. In the fifth group, consisting of allergic cases, no cases were treated. In 34 cases, cortisone eye drops and ointment were used in addition to subconjunctival injection. It is pointed out that many ocular conditions, such as interstitial keratitis, uveitis, and phlyctenular conjunctivitis, are due to reactions in the eye produced by stress in other parts of the body.

In eight cases of toxaemia of pregnancy, clinical improvement occurred out of all proportion to the changes in the blood pressure, albuminuria, and oedema. The oedema, however, frequently improved remarkably, while the effect on the blood pressure and albuminuria varied, with a tendency to fall. It was the authors' opinion that the patients became less liable to develop fits.

In general it was considered that cortisone had its greatest use in diseases of limited duration such as rheumatic fever, toxaemia of pregnancy, ophthalmic diseases, and some allergic conditions. The effect of cortisone had been studied on 142 patients up to February, 1951 (most of whom are not included in this preliminary report) including 88 eye cases, 29 of arthritis, four of rheumatic fever, and eight of toxaemia of pregnancy. An account of the physiological background of cortisone is included in this article. *R. Hodgkinson.*

The Effect of Continuous Intravenous Infusion of Adrenaline on the Circulation and Blood Chemistry. [In English.] PEKKARINEN, A., and HORTLING, H. (1951). *Acta endocrinol., Kbh.*, **6**, 193. 2 figs, bibl.

In order to determine the effect on the circulation and blood chemistry of continuous intravenous infusion, adrenaline was injected into the cubital vein of 25 hospital patients at an average rate of 0·2 μg. per kg. per minute for an average period of 52 minutes. The total amount of adrenaline averaged 0·65 mg. During the infusion and for the following 3 hrs the subjective and general symptoms were noted in twenty patients; in addition, the blood pressure, pulse rate, blood sugar level (Hagedorn-Jensen), and lactic acid content (Winnich), as well as serum phosphorus (inorganic), potassium (sodium-cobalt nitrite method), and cholesterol concentration, were determined.

The most noticeable subjective symptoms were palpitation, restlessness, tremor, and cold hands and feet. Respiration was normal as a rule. Following the infusion the head and upper part of the body felt warm. During the infusion the systolic pressure rose by an average of 16·5 per cent., whilst the diastolic pressure fell by some 9 per cent. The heart rate increased by 29 per cent., though the maximum value was not reached in many cases until the end of the infusion period. The effects on carbohydrate metabolism were pronounced. The blood sugar level rose by an average of 67 per cent., and the blood lactic acid concentration by 33 per cent., while the inorganic serum phosphorus level fell by 29 per cent. Contrary to the findings in animal experiments, the serum potassium level fell considerably (25 per cent.) during the infusion. A return to the initial values was noted within 1 hr after cessation of the infusion, and during the next few hours there were no changes indicating any marked deviation from the readings obtained in the control group. The control tests, however, revealed circulatory changes in some of the patients, indicating a state of mild excitement resulting from the test. The most remarkable results obtained were eosinopenia and lymphopenia, which developed 30 minutes to 2½ hrs after stopping the infusion. These changes suggest activation of the adrenal cortex resulting from the influence of adrenaline.

[The experiments were carried out to determine the circulatory and blood chemical effects in man of intravenous infusions of adrenaline in amounts which correspond approximately to the physiological secretion of adrenaline from the adrenals in a state of mild stress. Noradrenaline is liberated from the adrenals together with adrenaline, so that control experiments with noradrenaline, or mixtures of the amines, should have been carried out.] *G. B. West.*

Some Observations on the Physiologic Activity of $\triangle^{4:6}$-Dehydrocortisone (Diene). HIGGINS, G. M., WOODS, K. A., and KENDALL, E. C. (1951). *Endocrinology*, **48**, 175. 12 figs, 3 refs.

Cortisone acetate and $\triangle^{4:6}$-dehydrocortisone (a diene formed in small amount during the partial synthesis of cortisone acetate) were given singly and together in doses of 2 mg. intramuscularly for from 12 to 20 days to both intact and adrenalectomized adult male rats. The food intake of the treated adrenalectomized animals was well maintained, in contrast with the rapid decline of intake by the untreated adrenalectomized animals. Body-weight increase was much greater in the diene-treated animals than in those given cortisone alone or cortisone combined with diene, in spite of similar food intake. Even so, the diene did restrict growth to about 40 per cent. of that of the controls and accentuated the effects of cortisone in reducing body weight when both were given together. Whereas most of the untreated adrenalectomized rats were dead within 11 days, the treated adrenalectomized animals survived the experimental period of 19 days. Those which were given cortisone acetate lost, on an average, 32 g. in weight, whereas in those receiving the diene the average gain was 15 g.

In the intact rats cortisone induced marked leucopenia and lymphocytopenia, whereas there was a slight increase in total leucocytes and lymphocytes after diene; when both were given, the lymphocytopenia was less marked than after cortisone alone. In the adrenalectomized animals the lymphocyte count was higher than in the controls; it was reduced by 70 per cent. by cortisone, and, in contrast with the intact animals, by 40 per cent. by diene. The weight of the adrenals was reduced by 37 per cent. with cortisone, by 45 per cent. with diene, and by 51 per cent. with both together. In the intact rats the weight of the thymus gland was reduced by 67 per cent. with cortisone, by 52 per cent. with diene, and by 82 per cent. with both together. In the adrenalectomized animals there was an increase of 50 per cent.

in the weight of the thymus gland; this was reduced by 77 per cent. with cortisone and by 63 per cent. with diene.

In the cortisone-treated animals the lipid zone of the glomerulosa of the adrenal cortex was three times the width of that of the controls; the fat-staining zone of the fasciculata was less extensive than in the controls, but the fat droplets were more concentrated in the outer portion of the layer. Similar changes were found in the diene-treated animals, though the concentration of fat was somewhat less. The combination of cortisone and diene intensified the deposition of fat-staining lipids.

With cortisone there was stimulation of the thyroid gland, the epithelium becoming cuboidal and the colloid disintegrating; the diene also stimulated the epithelium but was without effect on the colloid; while the combination of the two had the same effects as cortisone alone. *Robert de Mowbray.*

Therapeutic Suppression of Tissue Reactivity. I. Comparison of the Effects of Cortisone and Aminopterin. GUBNER, R. (1951). *Amer. J. med. Sci.*, **221**, 169. 47 refs.

The author draws attention to the similarity between the therapeutic activity of cortisone and the folic acid antagonist which is termed aminopterin. The result of his researches seems to show that the locus of their biochemical effects is not the same. Both substances are none the less anti-anabolic and tend to inhibit tissue regeneration. He also reports evidence for believing that aminopterin exerts an additional inhibitory effect upon various specific tissue elements, since the lesions of psoriasis are much improved and experimental and clinical arthritis also respond favourably. This, he believes, reflects a suppression of both epithelial and mesenchymal activity.

The author considers that diseases of tissue reactivity should be grouped nosologically as such, since in such cases it is the tissue reactivity which itself constitutes the disease process, and therapy might be aimed at suppressing this. He discusses the question of compounds other than cortisone and aminopterin which may selectively affect mesenchyme. *W. S. C. Copeman.*

Effect of 17-Hydroxy-11-dehydrocorticosterone and Adrenocorticotropic Hormone upon Plasma Gamma Globulin, Fibrinogen, and Erythrocyte Sedimentation Rate. VAUGHAN, J. H., BAYLES, T. B., and FAVOUR, C. B. (1951). *Proc. Soc. exp. Biol., N.Y.*, **76**, 274. 4 figs, 13 refs.

The authors have examined 17-hydroxy-11-dehydrocorticosterone (cortisone) and adrenocorticotrophic hormone (ACTH) for their mechanism of action in relation to three blood elements. The observations were made on twelve hospital patients with severe, active rheumatoid arthritis, and three with actively progressing, generalized scleroderma. Blood samples were obtained before, during, and after one or more courses of 100 to 200 mg. of cortisone acetate (aqueous suspension) daily or 80 to 100 mg. ACTH daily. Both compounds were given intramuscularly in divided doses at 6-hour intervals.

It was found that during hormone treatment the average fall in plasma γ-globulin level was from 105 to 67 flocculation units, in that of fibrinogen from 8·3 to 4·9 mg. per ml. and in erythrocyte sedimentation rate from 1·16 to 0·59 mm. per second. The inter-relationships of the estimations in individual cases are discussed. The authors conclude that the sedimentation rate cannot be used as an index of the effectiveness of hormone therapy on the active disease process.

Malcolm Woodbine.

Observations on the Eosinophil Count in Man. A Proposed Test of Adrenal Cortical Function. FISHER, B., and FISHER, E. R. (1951). *Amer. J. med. Sci.*, **221**, 121. 5 figs, 14 refs.

A study has been made of the behaviour of eosinophil cells in man, with the object of determining the validity of the fall in eosinophil count after administration of adrenaline or ACTH as an indicator of adrenal function. Eosinophil counts were made, Hinkleman's solution being used as diluent stain. To establish normal eosinophil counts, 463 observations were made on 170 individuals. Wide scatter was found in resting values, only 50 per cent. of counts falling within the range of 100 to 250 per c.mm. found in normal subjects by Thorn. A large diurnal variation was found in individuals. Scatter diagrams are shown. On comparison, the total leucocyte and eosinophil counts showed no relationship.

After the injection of an adrenal cortical extract no consistent change in eosinophil count could be observed in 25 normal subjects. After injection of 0·3 mg. of adrenaline into 25 normal subjects there was a fall in 4 hours of 40 per cent. or more in 64 per cent. of the subjects, but a similar fall was also found in 23·5 per cent. of a control group. In four of the normal subjects there was a fall of less than 15 per cent. after adrenaline.

It is concluded that it is misleading to use fluctuations in the eosinophil count as a sensitive indicator of variations in activity of the adrenal cortex. *C. L. Cope.*

The Influence of Age, Sex, and Weight on the Daily Excretion of 17-Ketosteroids in Normal Subjects. (L'influenza dell'eta, del sesso e del peso sulla eliminazione giornaliera dei 17-chetosteroidi nei soggetti normali.) CIOFFARI, A., and COSSANDI, E. (1950). *Folia endocrinol., Pisa*, **3**, 637. 4 figs, 18 refs.

The 17-ketosteroids in a 24-hour specimen of urine were estimated in 140 normal people (77 males and 63 females) ranging from 18 months to 80 years of age; the patient being weighed at the same time. The distribution of the subjects over the 5-year age groups was fairly even from 1 to 80 years, the age groups up to 30 containing the larger number (75) of cases.

[This is a considerable feat, considering the difficulty of collecting a 24-hours' sample of urine in children up to 10 (31 cases).]

The conclusions are as follows. (1) The daily 17-ketosteroid excretion in the urine is influenced by age, being greatest between 20 and 40 years (12·5 mg.); after the age of 40 a gradual decline ensues to 7·5 mg. at 80. During the first 5 years of life it is very low (0·25 mg.), increasing to about 5 mg. at 10 years, and to 10 mg. at 15 years of age. (2) During the period of full sexual maturity, but especially between 20 and 40, men excrete considerably more than women; beyond 65 both sexes show a similar excretion (on a declining scale), provided their weight is equal; before puberty, there is no real difference between the sexes. (3) Body weight seems to have some [slight] influence on the daily excretion.

V. C. Medvei.

Endocrine Control of the Adrenal Gland. FELDMAN, J. D. (1951). *Anat. Rec.*, **109**, 41. 37 refs.

Injection of ACTH into intact rats produces hypertrophy of the adrenal glands with loss of carbonyl-positive, lipid, and birefringent material from the cortex. Hypophysectomy also causes loss of these materials and cortical atrophy in addition. The administration of thyroxine to intact rats causes adrenal hypertrophy, while thyroidectomy produces atrophy. In hypophysectomized rats, thyroxine has no effect on the adrenal. Growth hormone causes no change in the adrenal visible either macroscopically or microscopically.

Norval Taylor.

Cutaneous Side Effects of ACTH, Cortisone and Pregnenolone Therapy. BRUNNER, M. J., RIDDELL, J. M., and BEST, W. R. (1951). *J. invest. Derm.*, **16**, 205. 3 figs, 7 refs.

The cutaneous side-effects of treatment with ACTH, cortisone, a combination of these, and with pregnenolone are reported. Daily dosage was from 50 to 100 mg. ACTH, 50 to 200 mg. cortisone, and 100 to 150 mg. pregnenolone. There were 105 patients whose ages varied from 18 months to 85 years. Noteworthy side-effects were not observed in 26 patients treated with ACTH or cortisone for less than 2 weeks. Of 79 treated for longer, forty patients (51 per cent.) showed cutaneous side-effects, of which hyperpigmentation (in 29) was most common. Acne was seen in 26 patients. Only those treated with ACTH showed hypertrichosis, of whom eleven were women and one a pre-adolescent boy. In three patients seborrhoeic dermatitis was seen, though there was increased oiliness of the skin in others. Of the patients with seborrhoeic dermatitis, one was under treatment with pregnenolone and supplied the only example of a side-effect with this substance. " Moon face " was seen in eleven of 41 patients treated with ACTH alone.

A detailed report is given of one patient receiving ACTH who had severe skin reactions (acne, pigmentation, and " moon face ").

S. T. Anning.

The Effects of Adrenocorticotropic Hormone and Cortisone in the Adrenogenital Syndrome associated with Congenital Adrenal Hyperplasia: an Attempt to explain and correct its Disordered Hormonal Pattern. BARTTER, F. C., ALBRIGHT, F., FORBES, A. P., LEAF, A., DEMPSEY, E., and CARROLL, E. (1951). *J. clin. Invest.*, **30**, 237. 13 figs, 25 refs.

This paper from the Massachusetts General Hospital describes detailed metabolic studies on three female children suffering from the adrenogenital syndrome. In many respects these patients showed an abnormal response following the administration of ACTH. There was no significant increase of urinary 11-oxysteroids, and the patients did not develop a negative nitrogen balance or show a reduction of circulating eosinophils. There was also a failure to develop sodium and chloride retention. The urinary 17-ketosteroid content, however, definitely rose. These findings suggested that in this syndrome the adrenal cortex is unable to respond normally to ACTH by increased production of " carbohydrate-active " and " salt-retaining " steroids, but that it is capable of a response by producing androgens.

Administration of cortisone acetate (100 mg. daily for 12 days) to two patients produced a markedly negative nitrogen balance and a fall of urinary 17-ketosteroid level to normal. The authors believe that the action of cortisone on the 17-ketosteroid excretion was due to depression of pituitary ACTH production. It is postulated that the adrenal androgens inhibit ACTH production relatively weakly, whereas " sugar hormone " inhibits ACTH production relatively strongly. If then the adrenal production of sugar hormone is deficient, pituitary ACTH production is not depressed and more ACTH is secreted. This in turn leads to an overproduction of adrenal androgen. Both these patients were subsequently given a prolonged course of cortisone (50 to 100 mg. twice weekly). At the time of writing (6 months) the urinary ketosteroids had been maintained at normal levels, but it was too early to decide whether further virilism could be prevented by this therapy.

G. Ansell.

Effect of Antihistamine Drugs on the Adrenal Cortical Response to Histamine and to Stress. TEPPERMAN, J., RAKIETEN, N., BIRNIE, J. H., and DIERMEIER, H. F. *J. Pharmacol.*, **101**, 144. 5 figs, 16 refs.

The authors sought to discover whether the activation of the pituitary-adrenal system produced by the injection of histamine could be blocked by pre-treatment with antihistamine drugs. The experiment was performed on 200 adult albino rats with a mean weight of 240 g. The antihistamine drugs were tripelennamine, diphenhydramine, and " phenoxadine " in doses that were approximately equimolar (30, 30, and 50 mg. respectively per kg. body-weight.) The amount of ACTH released was estimated indirectly by the renal ascorbic acid depletion technique. An intraperitoneal injection of histamine phosphate in a dosage of 10 mg. per kg. bodyweight produced a significant fall in adrenal ascorbic acid content. A partial diminution of this response was achieved by previous treatment with phenoxadine.

In a further experiment with the photo-electric tensometer technique of studying blood-pressure responses in unanaesthetized rats, phenoxadine was shown to prevent the hypotensive action of histamine when given one hour before administration of the histamine in a dose of 50 mg. per kg. When the dose of histamine was increased to 100 mg. per kg. it was found that not even the highest dose of phenoxadine would prevent the fall in blood pressure.

These experiments were repeated with the other two drugs. It was established that the administration of these antihistamine drugs did not in itself cause any significant change in adrenal ascorbic acid content in the rat, whereas histamine reduced it from 400 mg. per 100 kg. to 277 mg. per 100 kg. tissue. Histamine injection one hour after pre-treatment with phenoxadine or tripelennamine resulted in a smaller fall in adrenal ascorbic acid content than in controls. Pre-treatment with diphenhydramine, however, did not modify the response to histamine injection, nor did pre-treatment with any of the antihistamine drugs prevent the reduction in adrenal ascorbic acid content in response to an intraperitoneal injection of carbon tetrachloride.

R. Hodgkinson.

Use of Cortisone in Diseases of the Eye. LAVERY, F. S., WERNER, L. E., O'DONOGHUE, S., GUINAN, P. M., and MACDOUGALD, J. (1951). *Brit. med. J.*, **1**, 1285. 1 table, 6 refs.

Trials of the effect of cortisone in ocular disease were begun in Dublin in July, 1950, and this report consists of grouped clinical notes of 21 types of lesions, more detailed notes of six cases, and references to results in a further series of fifty.

Cortisone was administered as ointment (25 mg. per g.), as drops of the undiluted suspension, and by subconjunctival injection, either separately or combined. The results confirm, to some extent, American reports of the effectivity of this form of treatment: little effect was seen in corneal dystrophy, exudate macular conditions, retinal detachment, choroiditis, and scleritis. The two last-named conditions were seen to respond well, however, when cortisone was given systemically. In iridocyclitis, where the results generally were found to be good, the importance of early treatment is stressed. Ocular pemphigus, also in the early stage of active bullae, responded well as far as subjective symptoms and symblepharon were concerned; but corneal opacity was unaffected. Eight of nine cases of interstitial keratitis (syphilitic) were particularly benefited and in the single case of disciform keratitis the corneal opacity was reduced to one quarter of its original size within two weeks of treatment. In two cases of fresh lime burns, however, the treatment appeared to be without effect whilst in corneal ulcers, apart from some subjective relief of symptoms, the condition appeared to be uninfluenced.

Beneficial effects upon post-operative irritation and inflammation have prompted the authors to give a trial to prophylactic injections, given on the table immediately after operation. They conclude that cortisone is very valuable in the control of allergic reactions in the eye.

H. E. Hobbs.

Clinical Experiences with ACTH and Cortisone in Ocular Diseases. MCLEAN, J. M., GORDON, D. M., and KOTEEN, W. (1951). *Trans. Amer. Acad. Ophthal. Otolaryng.*, **55**, 565.

The Effect of Cortisone on Experimental Inflammation of the Rabbit Anterior Chamber caused by Sterile Talc Powder. (Influence de la cortisone sur l'inflammation expérimentale de la chambre antérieur du lapin, causée par de la poudre de talc stérile.) BOURQUIN, J. B. (1951). *Experientia, Basel*, **7**, 229. 13 refs.

The Present Status of ACTH and Cortisone in Clinical Ophthalmology. WOODS, A. C. (1951). *Amer. J. Ophthal.*, **34**, 945. 5 tables, 12 refs.

Clinical Observations on the Use of Cortisone in Ophthalmic Diseases. HENDERSON, J. W., and HOLLENHORST, R. W., (1951). *Trans. Amer. Acad. Ophthal. Otolaryng.*, **55**, 543.

Clinical and Experimental Observations on the Use of ACTH and Cortisone in Ocular Inflammatory Disease. WOODS, A. C. (1950). *Trans. Amer. ophthal. Soc.*, **48**, 259. 23 figs, 19 refs.

ACTH and Cortisone in Ophthalmology. HILL, H. F., DENNIS, R. H., and SHANNON, C. E. G. (1951). *J. Maine med. Ass.*, **42**, 47.

First Trials of ACTH and Cortisone. (Premiers essais avec l'ACTH et la cortisone.) HARTMANN, E., MORAX, P. V., and PINCHON, S. (1950). *Bull. Soc. Ophtal. France*, **9**, 739.

Improvement of a Case of Sympathetic Ophthalmitis by ACTH. (Amélioration d'une ophtalmie sympathique par l'ACTH.) JOSEPH, E., OFFRET, G., and FOREST (1950). *Bull. Soc. Ophtal. France*, **9**, 756.

Case report. *J. Rougier.*

Recurrent Choroiditis treated with Cortisone. GUINAN, P. M. (1951). *Brit. J. Ophthal.*, **35**, 431. 2 refs.

Sympathetic Ophthalmia treated successfully with ACTH. LAWS, H. W., and HOWARD, R. P. (1951). *Canad. med. Ass. J.*, **64**, 530. 1 ref.

Cortisone in Sympathetic Ophthalmitis. (La cortisone dans l'ophtalmie sympathique.) MOUTINHO, H. (1950). *Bull. Soc. Ophtal. France*, **8**, 652.

First Trials of Treatment of Iridocyclitis by Cortisone. (Premiers essais de traitement des iridocyclites par la cortisone à l'Hôtel-Dieu.) DESVIGNES, P., FONTAINE, and MORAULT, Y. (1950). *Bull. Soc. Ophtal. France*, **9**, 776.

Present Status of ACTH and Cortisone in Treatment of Eye Diseases. MCLEAN, J. M. (1951). *Sight-Sav. Rev.*, **21**, 67.

Effect of Cortisone on Experimental Herpes-Simplex Keratitis of the Rabbit. THYGESON, P., GELLER, H. O., and SCHWARTZ, A. (1951). *Amer. J. Ophthal.*, **34**, 885, 14 refs.

Eales's Disease treated with Cortisone, Streptomycin, and Vitamin C. MAHON, D. (1951). *J. Irish med. Ass.*, **28**, 50.

Cortisone in Ocular Diseases. (Emploi de la cortisone dans les affections oculaires.) MICHAUD, P., and FORESTIER, J. (1950). *Bull. Soc. Ophtal. France*, **9**, 764. 9 refs.

Constitutional Factors in Resistance to Infection: the Effect of Cortisone on the Pathogenesis of Tuberculosis. LURIE, M. B., ZAPPASODI, P., DANNENBERG, A. M., and SWARTZ, I. B. (1951). *Science*, **113**, 234. 7 refs.

The Effect of Adrenocorticotrophic Hormone (ACTH) on Experimental Tuberculosis in Mice. Preliminary Report [In English.] SWEDBERG, B., DAHLSTRÖM, G., and LUFT, R. (1951). *Acta endocrinol., Kbh.*, **6**, 215. 2 refs.

Effect of Cortisone, Deoxycortone Acetate, and Artisone on the Healing of Experimental Skin Wounds. (Effetto del cortisone, del DCA e dell'artisone sulla guarigione delle ferite cutanee sperimentali.) CAVALLERO, C., BORASI, M., SALA, G., and AMIRA, A. (1951). *Arch. int. Pharmacodyn.*, **86**, 43. 2 figs, 13 refs.

Cortisone-treated Scleroderma. Report of a Case with Autopsy Findings. SHARNOFF, J. G., CARIDEO, H. L., and STEIN, I. D. (1951). *J. Amer. med. Ass.*, **145**, 1230. 4 figs, 8 refs.

Some Observations on the Use of Adrenocorticotropic Hormone in Atopic Dermatitis in Infancy. DIGEORGE, A., and NELSON, W. E. (1951). *J. Pediat.*, **38**, 164. 4 refs.

Adrenocorticotropic Hormone (ACTH): its Effect in Atopic Dermatitis. RANDOLPH, T. G., and ROLLINS, J. P. (1951). *Ann. Allergy*, **9**, 1 and 18. 9 figs, 13 refs.

Effect of ACTH in Acute Dermatomyositis. SUZMAN M. M., and RUDOLPH, J. A. (1951). *Lancet*, **1**, 660 1 fig., 4 refs.

The Effect of Cortisone on the Clinical Course of Chronic Regional Enteritis and Chronic Idiopathic Ulcerative Colitis. MACHELLA, T. E., and HOLLAN, O. R. (1951). *Amer. J. med. Sci.*, **221**, 501. 2 figs, 4 refs.

Effect of Cortisone on Acute Streptococcal Infections and Post-streptococcal Complications. HAHN, E. O., HOUSER, H. B., RAMMELKAMP, C. H., DENNY, F. W., and WANNAMAKER, L. W. (1951). *J. clin. Invest.*, **30**, 274. 4 figs, 32 refs.

Treatment of Ulcerative Colitis and Regional Enteritis with ACTH. Significance of Fecal Lysozyme. GRAY, S. J., REIFENSTEIN, R. W., BENSON, J. A., and YOUNG, J. C. G. (1951). *Arch. intern. Med.*, **87**, 646. 4 figs, 7 refs.

The Treatment of Acquired Hemolytic Anemia with Adrenocorticotrophic Hormone (ACTH). DAMESHEK, W., ROSENTHAL, M. C., and SCHWARTZ, L. I. (1951). *New Engl. J. Med.*, **244**, 117. 5 figs, 30 refs.

Treatment of Typhoid Fever. I. Combined Therapy with Cortisone and Chloramphenicol. SMADEL, J. E., LEY, H. L., and DIERCKS, F. H. (1951). *Ann. intern. Med.*, **34**, 1. 1 fig., 15 refs.

Treatment of Typhoid Fever. II. Control of Clinical Manifestations with Cortisone. WOODWARD, T. E., HALL, H. E., DIAS-RIVERA, R., HIGHTOWER, J. A., MARTINEZ, E., and PARKER, R. T. (1951). *Ann. intern. Med.*, **34**, 10. 4 figs, 9 refs.

Effect of Cortisone in Sarcoidosis. SONES, M., ISRAEL, H. L., DRATMAN, M. B., and FRANK, J. H. (1951). *New Engl. J. Med.*, **244**, 209. 6 figs, 8 refs.

Adrenal Cortex Extract in Pediatrics. Possible Effect on the Respiratory System of the Newborn. PROVENZANO, R. W., MCGOVERN, P., SCHULTZ, R. (1951). *Amer. J. Dis. Child.*, **81**, 323. 1 fig., 11 refs.

General Pathology

The Morbid Histology of the Muscles in Rheumatoid Arthritis. (Sull'istopatologia dei muscoli nella poliartrite cronica primaria.) GALLI, T., and MORIN, F. (1951). *Rev. Rhum.*, **12**, 59. 7 figs, 21 refs.

The authors give an excellent review of previous work in this field and detail the various views held as to the pathogenesis of the nodules which occur in rheumatic conditions. They have studied eleven cases of rheumatoid arthritis, performing muscle biopsies in all. The technique used is described, and clinical details and histological findings (with photomicrographs) are given of each case. The findings were similar in all cases and are in agreement with those of other workers, although more importance is attached to the changes in the muscle fibres. The small-celled infiltrations in the connective tissue are considered to be similar to those found in other "collagen diseases", whether in many tissues as in disseminated lupus erythematosus and diffuse scleroderma, or localized as in thromboangiitis obliterans or periarteritis nodosa. The lesions in the muscle fibres consist in changes in the number of nuclei, varying from a very slight increase to a great increase, with nuclei forming masses. The various grades of change are thought to be purely quantitative. It had been hoped to prove that muscle biopsies are as useful a diagnostic aid in rheumatoid arthritis as sternal puncture is in haematology, but the conclusion is reached that the changes found are not specific, but are due to muscular atrophy and can be found in other conditions causing such atrophy.

R. F. Jennison.

Response of the Serum Hyaluronidase Inhibitor and Mucoproteins to Adrenocorticotropic Hormone in Rheumatic States. Mucolytic Enzyme Systems. XV. ADAMS, F. H., KELLEY, V. C., DWAN, P. F., and GLICK, D. (1951). *Pediatrics*, **7**, 472. 7 figs, 25 refs.

Adrenocorticotrophic hormone was given, in doses of 40 to 100 mg. daily for an average of about 4 weeks, to thirteen patients with acute rheumatic fever and two with juvenile rheumatoid arthritis: the ages of the patients ranged from 4 to 17 years. Prompt relief of their acute symptoms was observed.

The levels of the serum non-specific hyaluronidase inhibitor and of the serum mucoprotein-tyrosine were especially studied. It was found that the hyaluronidase-inhibitor level fell rapidly during the administration of ACTH, reaching normal usually in 10 to 15 days and often becoming subnormal subsequently. This followed the fall in the erythrocyte sedimentation rate, and the subjective improvement in the patient's condition. The fall in the serum mucoprotein level was much slower, and normal values were usually not seen for 3 or 4 months. This is in contrast to the findings in patients who have not received ACTH, but are treated symptomatically: in these the serum level of mucoprotein and of hyaluronidase inhibitor fall at about the same rate. If ACTH was withdrawn or reduced in dose before the serum mucoprotein level fell substantially, there was a recurrence of the disease, even if the sedimentation rate and hyaluronidase-inhibitor level had returned to normal.

One patient had diabetes mellitus in addition to rheumatic fever. ACTH therapy necessitated an increase in the dose of insulin from 40 to 80 units daily. The clinical response was good, and similar to that of other patients: after ACTH was discontinued, the insulin requirements gradually returned to their former level.

Mild acne and slight fluid retention, not amounting to pitting oedema, were the only side-effects noted.

B. E. W. Mace.

Delay of the Early Inflammatory Response by Cortisone. MICHAEL, M., and WHORTON, C. M. (1951). *Proc. Soc. exp. Biol., N.Y.*, **76**, 754. 1 fig., 3 refs.

The effect of cortisone on the earliest tissue phases of the inflammatory reaction in the skin of rabbits was studied. A combination of croton oil and scarification was used as the inflammatory stimulus. In animals given cortisone, all of the tissue components of the inflammatory reaction were delayed, and some were quantitatively reduced. Vascular margination of leucocytes, migration of leucocytes from blood vessels, and the formation of fibrin and edema were strikingly altered. The ultimate development of necrosis was diminished. The relationship of these observed facts to the enhancing effect of cortisone and ACTH on certain bacterial infections is suggested.—[*Authors' summary.*]

Rheumatism as an Experimental Pathological Problem. (Rheumatismus als Problem der experimentellen Pathologie.) STUDER, A. (1951). *Z. Rheumaforsch.*, **10**, 65. 12 figs, bibl.

A Study of the Antigen-Antibody Mechanism in Rheumatic Diseases. BROWN, T. M., WICHELHAUSEN, R. H., MERCHANT, W. R., and ROBINSON, L. B. (1951). *Amer. J. med. Sci.*, **221**, 618. 3 figs, bibl.

Liver Function Tests in Nonspecific Arthritis with Special Reference to Hyperglobulinemia. ARCHER, B. H. (1951). *Ann. intern. Med.*, **34**, 1173. 24 refs.

The Role of the Pleuro-pneumonia-like Organism in Venereal Rheumatism. (Rôle des "organismes L" dans les rheumatismes vénériens.) DUREL, P., ROIRON-RATNER, V., and BOREL, L. J. (1951). *Pr. méd.*, **59**, 789. 39 refs.

Granulomatous Glomerulonephritis associated with Polyarthritis. Report of a Case. MCMANUS, J. F. A., and HORNSBY, A. T. (1951). *Arch. Path. Chicago*, **52**, 84. 2 figs, 11 refs.

Other General Subjects

Acute and Subacute Disseminated Lupus Erythematosus. A Correlation of Clinical and Postmortem Findings in Eighteen Cases. GRIFFITH, G. C., and VURAL, I. L. (1951). *Circulation*, **3**, 492. 4 figs, 18 refs.

A short review of the literature and of the lesions seen in acute and subacute disseminated lupus erythematosus is given in addition to the findings in 18 cases. The authors confirmed the predominance of the disease in females and its highest incidence in the second and third decades of life. Joint pains were present in 72·2 per cent. of cases and preceded the skin lesions, which occurred almost as frequently. Fever, tachycardia, and dyspnoea were most often accompanied by albuminuria, anaemia, leucopenia, and hyperglobinaemia. The diagnosis was confirmed either by skin biopsy or by the finding of lupus erythematosus cells in the peripheral blood or the bone marrow. *G. J. Cunningham.*

The L.E. (Lupus Erythematosus) Cell. Clinical and Chemical Studies. LEE, S. L., MICHAEL, S. R., and VURAL, I. L. (1951). *Amer. J. Med.*, **10**, 446. 5 figs, 11 refs.

The lupus erythematosus (L.E.) cell was found in the peripheral blood and bone marrow in every proved case of acute disseminated lupus erythematosus examined. Cases of diffuse vascular disease, rheumatoid arthritis, dermatomyositis, scleroderma, and rheumatic heart disease (active and inactive) were examined with negative result. The authors showed also that use of an anticoagulant is not necessary, and that time was probably the factor required, for activation of the plasma fraction responsible for producing the L.E. cell. The inclusion material in the L.E. cells was found to stain with Feulgen and methyl-green stains, thus establishing its content of desoxyribose nucleic acid; from the Feulgen : methyl-green ratios it is concluded that the desoxyribose nucleic acid is in a dipolymerized state. The methods of examination adopted are described. *A. Brown.*

Systemic Lupus Erythematosus. Some Cutaneous Manifestations related to the Diffuse Collagenous Diseases. SHAFFER, B., JAMES, G. W., SCULLY, J. P., and PILLSBURY, D. M. (1951). *Amer. J. med. Sci.*, **221**, 314. 20 refs.

Three cases of systemic lupus erythematosus are described and discussed. A woman of 25 first developed the chronic discoid variety of the disease; this was followed by attacks of the acute disseminated variety and, on one occasion, by lesions of the profundus type. Other lesions appeared which closely resembled papulonecrotic tuberculides, erythema nodosum, and periarteritis nodosa. There were multiple chronic foci of infection. Intracutaneous tests with very low concentrations of *Staphylococcus aureus haemolyticus*, *Streptococcus haemolyticus*, and *Strep. viridans* all showed marked sensitivity. (2) A woman of 38 had suffered from Raynaud's syndrome since the age of 16. She had evidence of old lung and kidney infections. Chronic discoid lupus erythematosus was followed by a scarlatiniform eruption attributed to taking sulphonamides. Later there appeared erythema nodosum, obliteration of the left ulnar artery, and fluffy exudates in the fundus of the left eye. (3) A woman of 27, had fulminating disseminated lupus erythematosus. There were raised blood pressure, an erythemato-papular rash, retinopathy, nephritis, adhesive pericarditis, endocarditis and purpura. Post-mortem examination revealed marked degeneration of the adrenal glands.

All the conditions described are primarily vascular changes brought about by hyperergic reactivity to many antigens. Sunlight and sulphonamides may act as precipitating factors. The important role of the adrenal cortex in vascular physiology, and the remissions which may result from cortisone therapy suggest that the vascular system is the fundamental site of this disease.

E. Lipman Cohen.

The Pathology of Collagen Disease applied to the Eye. CHRISTENSEN, L. (1951). *Trans. Amer. Acad. Ophthal. Otolaryng.*, **55**, 536.

The author discusses the structure and distribution of collagen and the pathological changes occurring in the collagen disease. Collagen disease in the eye involves primarily either the ocular coats or vessels; primary

lesions occur in the cornea, sclera, retina, and uveal tract. It is possible that the corneal ulcers occurring in acne rosacea may be focal areas of fibrinoid degeneration in the corneal stroma.

Scleritis, episcleritis, and scleromalacia perforans are collagen diseases occurring in the ocular coats, whilst the uveitis associated with rheumatoid arthritis and the choroidal and retinal lesions occurring in polyarteritis nodosa are examples of vascular involvement.

The author considers that the cytoid body occurring in the retina is in all probability a fibrinoid degeneration involving neural tissue. Collagen may be considered as a structural tissue element, normally existing as a dynamic colloidal system and probably subject to hormonal control. Pathological alteration of this system by an aetiological factor such as hypersensitivity gives rise to collagen diseases. *C. A. Cook.*

The Ocular Manifestations of the Diffuse Collagen Diseases. HOLLENHORST, R. W., and HENDERSON, J. W. (1951). *Amer. J. med. Sci.*, **221**, 211.

The authors felt that the frequent presence of ocular manifestations in these diseases warranted further study of how they resembled or differed from each other. Their work did not imply that there was a common aetiology or interrelationship in these diseases. Histologically, however, they all attacked the connective and vascular tissues. The diseases considered were serum sickness, lupus erythematosus, periarteritis nodosa, dermatomyositis, temporal or cranial arteritis, Schönlein-Henoch purpura, thromboangiitis obliterans, rheumatoid arthritis, rheumatic fever, and scleroderma. A table of the ocular manifestations of these diseases is shown. All the diseases except scleroderma could result in serious impairment of vision because of the toxic retinopathy which they were capable of producing. None of the ocular tissues or eyelids escaped, though not all were attacked in every disease.

Since ACTH and cortisone have proved so beneficial, the effects of therapy and the progress or remission of these diseases have been much better understood because the internal ocular tissues could be seen and studied as the treatment was carried out. In most cases of dermatomyositis, disseminated lupus erythematosus, serum sickness, and in many cases of periarteritis nodosa, ocular lesions are absent, but it is suggested that a complete ocular examination including ophthalmoscopy be performed where a collagen disease is suspected. If a collagen disease is diagnosed the eye examination should be repeated frequently. *Francis M. Crage.*

Rheumatism in the Miner. (Bergmann und Rheuma.) BAADER, E. W. (1951). *Z. Rheumaforsch.*, **10**, 135. 1 fig.

This contribution which, comes from Bad Hamm, where the Ruhr coal miners have a hospital equipped with warm mineral baths containing 8 per cent. sodium chloride, is based on observations made on 4,500 miners. The author complains that more than 1,000 patients have been sent in with wrong diagnoses due either to lack of *x*-ray investigation or to the cursory nature of the physical examination.

The " climate " of the pit is the result of the temperature, the relative humidity, and the air-stream. The most frequent rheumatic diseases in the miner are sciatica, lumbago, osteo-arthritis of the lumbar and cervical spine, brachial neuritis, fibrositis, ankylosing spondylitis, and humero-scapular periarthritis, in descending order of incidence. Acute rheumatic fever has rarely been encountered.

The author stresses the following points. In 11·5 per cent. of cases of sciatica the cause was found to be a disk lesion, a very high proportion according to the author [but low according to British and American literature], the remainder being due to osteo-arthritis around the vertebral foramina. Lumbago is divided into muscular and osseous forms, according to negative or positive *x*-ray findings: the latter group show osteo-arthritic changes. Brachial neuritis may be caused not only by the climatic conditions in the mine, but by mechanical injuries resulting from the use of pneumatic drills.

To counteract the harmful conditions in the mine the author suggests: (1) that miners should be provided with a coat against the draught, to be worn between the working place and the wash room; (2) that miners should not have to sit on iron in the waggon; (3) that warm douches should alternate with a cold stream as a stimulus for capillary tone. *J. Mester.*

Post-operative Stenosis of the Large Bowel Caused by Periarteritis Nodosa. (Post operative Dickdarmstenose durch periarteriitis nodosa.) FRIEDEBOLD, G. (1950). *Zbl. Chir.*, **75**, 1753. 2 figs, 7 refs.

Benign obstruction of the large bowel is uncommon. An instance is described of obstruction caused by the swelling due to localized periarteritis nodosa at the site of a former gut resection for carcinoma.

A woman, aged 62, was operated on for carcinoma of the sigmoid in the summer of 1946, when resection was successfully performed; in April, 1948, she returned with symptoms of recurrent obstruction of the large bowel; caecostomy was performed and at the same time a movable mass was felt at the site of the former anastomosis. While waiting for further operation the patient had a septic temperature-curve with a normal pulse rate, and at the same time there was general jaundice which gradually disappeared. When the fever subsided, operation was undertaken; the mass at the site of the former anastomosis was resected, but the posterior wall of the anastomosis was preserved and the bowel reconstituted. There was no sign of any malignant secondary in the abdomen. The resected mass, as well as tissue excised at the time of closure of the caecostomy and the appendix, showed the microscopical appearances of periarteritis nodosa. The patient was well 2 years later, but had some paraesthesia of the extremities.

It is pointed out that though the pathological course of periarteritis nodosa is that of one disease process, yet the clinical picture depends upon the viscera involved, and the diagnosis can scarcely be made with surety unless biopsy be performed. The condition must be considered in the diagnosis of all cases of chronic sepsis, polyneuritis, or polymyositis which are associated with disturbances of the heart, kidneys, liver, or stomach. *Zachary Cope.*

Fibrous Dysplasia of Bone. (Displasia fibrosa de los huesos.) VALLS, H., and SCHAJOWICZ, F. (1950). *Rev. Ortop. Traum.*, **20**, 83. 33 figs, bibl.

In this careful study of 26 cases of monostotic and polyostotic fibrous dysplasia of bone the authors have

not found proof for the theory of Thannhauser (*Medicine*, 1944, **23**, 105) that such dysplasia is closely related to neurofibromatosis. A large number of fine photomicrographs of the structural elements of these localized dysplasias does not exhibit nervous elements similar to those seen in neuro-fibroma. There is a [rather incomplete] survey of the literature, followed by a description of the method of investigation and a somewhat detailed survey of the cases with illustrations of *x*-ray and pathological findings.

[It is a pity that so much painstaking work is still wasted on attempts to prove or disprove theories concerning pathogenesis by histological methods. The abstracter (*Ergebn. Chir. Orthop.*, 1933, **26**, 328) took this view in a detailed study of osteitis fibrosa, restated in more general terms in the *Lancet* (1939, **1**, 186.)]

L. Michaelis.

Reiter's Syndrome in Childhood. CORNER, B. D. (1950). *Arch. Dis. Child.*, **25**, 398.

A case in a child aged 9 years is reported which followed an injection with *Sh. flexneri V*. The syndrome should be borne in mind after epidemics of dysentery.

S. J. H. Miller.

The Permeability of the Synovial Membrane. (La perméabilité synoviale.) COSTE, F., and BOUREL, M. (1951). *R.C. Ist. sup. San.*, **14**, 32. 15 figs, bibl.

The Rheumatic Diseases. COHEN, H. (1951). *J. roy. sanit. Inst.*, **71**, 296.

The Incidence of Rheumatic Conditions. (De frequentie van rheumatische aandoeningen.) BARUCH, J. Z. (1951). *Tijdschr. soc. Geneesk.*, **29**, 255. 11 refs.

Focal Infection and the Rheumatic Diseases. GRAHAM, W. (1951). *Int. dent. J.*, **1**, 111.

Gonococcal Rheumatism. (Rhumatisme gonococcique.) CAMUS, J. P. (1951). *Gaz. méd. France*, **58**, 453.

Renal Rheumatism. (Reumatismo renal.) MORÁN MIRANDA, F. (1951). *Prensa méd. argent.*, **38**, 969. Bibl.

The Ocular Manifestations of Rheumatism. (A propos des manifestations oculaires du rhumatisme.) MAIGNIEN-COURARD, A. (1951). *Gaz. méd. France*, **58**, 445. 18 refs.

Rheumatism—Unitary Conception and Control by Modern Methods. GOOD, M. G. (1951). *J. Lancet*, **71**, 93. 7 figs, 12 refs.

The Rheumatism Problem. (Rheumatismus-Problem.) VON MUNDY, V. G. (1951). *Med. Klinik.*, **46**, 110.

Multicentric Osteogenic Sarcoma in Paget's Disease with Cerebral Extension. DERMAN, H., PIZZOLATO, P., and ZISKIND, J. (1951). *Amer. J. Roentgenol.*, **65**, 221. 11 figs, 12 refs.

Reiter's Syndrome. MCLACHLAN, A. E. W. (1951). *Bristol med.-chir. J.*, **68**, 87. 10 refs.

Rheumatic Conditions of the Lungs and Pleura. (Affezioni pleuropulmonari di natura reumatica.) PANCINO, G. (1950). *G. Sci. med.*, **5**, 128.

Radiological Diagnosis of Chronic Rheumatism. STEVEN, G. D. (1951). *Med. Pr.*, **113**, 655.

Rheumatism in Temperate Climates. Personal Experience in Teneriffe, Canaries. (La enfermedad reumática en los climas templados. Experiencia personal en Tenerife, Canarias.) CERVIA, T. (1951). *Rev. argent. Reum.*, **15**, 225. 27 refs.

Rheumatism in the Moslem Child. Effect of Social Factors on its Development. (La maladie rhumatismale de l'enfant musulman. Incidence des facteurs sociaux sur son développement.) SARROUY, C., and VENEZIA, R. (1951). *Bull. Acad. nat. Méd., Paris*, **135**, 91. 5 refs.

Standardization of Observations in Rheumatism. (Schemas d'observations rhumatologiques.) LIÈVRE, J. A. (1951). *Rev. Rhum.*, **18**, 117. 11 refs.

Team-work in the Rheumatic Diseases. FISHER, A. G. T. (1951). *Brit. J. phys. Med.*, **14**, 169.

The Relationship between Subacute Rheumatism, Tuberculosis, and Tonsillitis. (Sui rapporti fra reumatismo sub-acuto, tubercolosi e tonsille.) VALLECORSI, G. (1951). *Settim. med.*, **39**, 38. 1 fig, 17 refs.

The Spa Treatment of Rheumatism. (Mémoire sur la crenothérapie du rhumatisme.) EYDIEUX, H. (1951). *Arch. Méd. soc.*, **7**, 69.

The Bed Problem in the Campaign against Rheumatism. (Het " beddemprobleem " bij de rheumabestrijding.) DE BLÉCOURT, J. J. (1951). *Tijdschr. soc. Geneesk.*, **29**, 258.

Analgesics in the Treatment of Chronic Rheumatism. (Médications antialgiques des rhumatismes chroniques.) TRUET, —. (1951). *Gaz. méd. France*, **58**, 465.

The Treatment of Rheumatism with Rutin and Ascorbic Acid. (Tratamiento de la enfermedad reumática con rutina y acido ascorbico.) SCHNIR, M. (1951). *Rev. argent. Reum.*, **15**, 232. 30 refs.

The Effects of 17-ketosteroid Deficiency and Male Hormone Therapy in Rheumatic Fever and Arthritis. DUNN, C. W. (1951). *Delaware med. J.*, **23**, 36. 2 figs, 4 refs.

Aspirin and Salicylates. Current Views on their Biological Action. (Aspirine et salicylates; vues actuelles sur leurs actions biologiques.) MARCHE, J. (1951). *Gaz. méd. France*, **58**, 421. Bibl.

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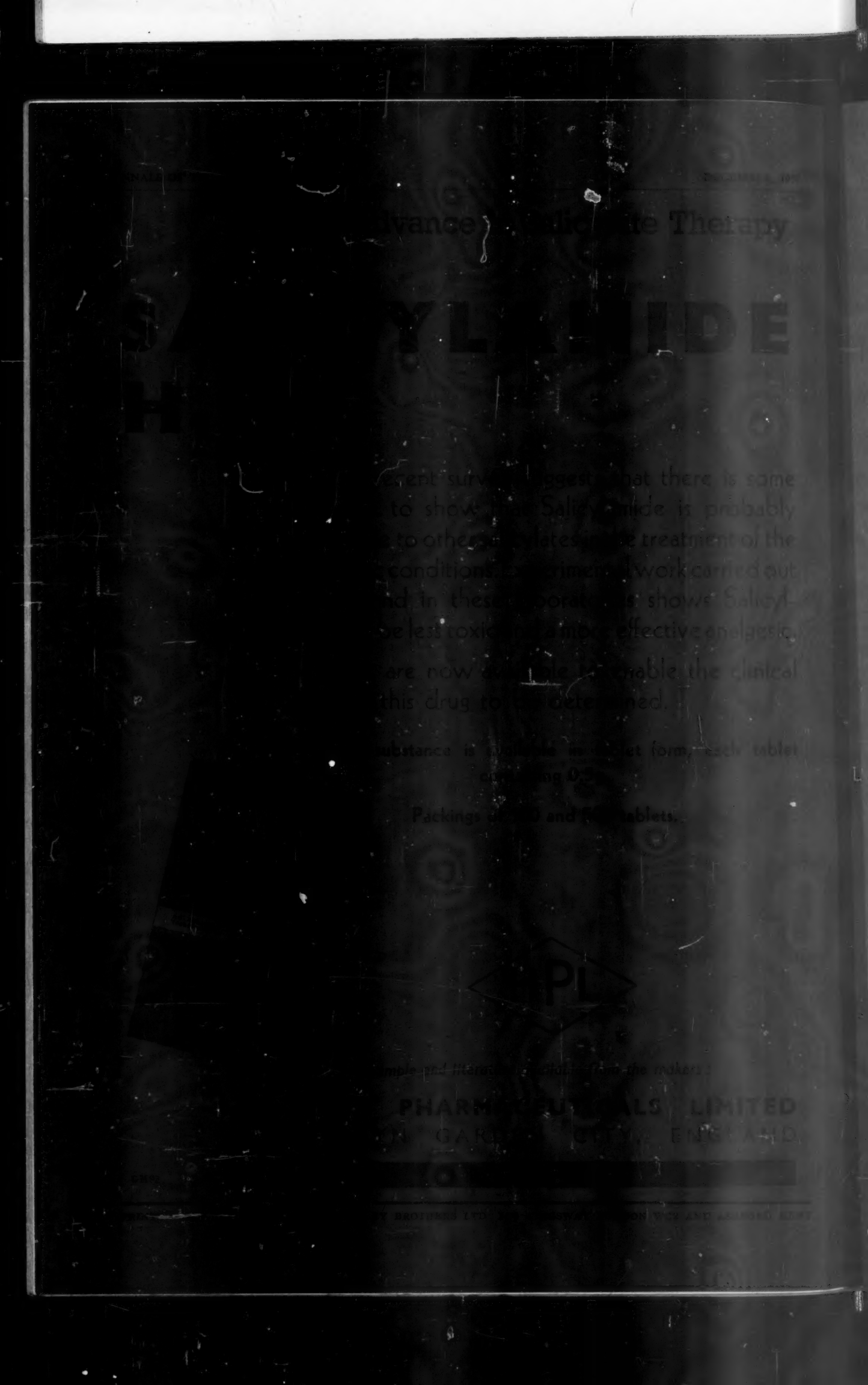
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